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Studies on Biologically Active Halogenated Compounds. 1. Synthesis and Central Nervous System Depressant Activity of 2-(Fluoromethyl)-3-aryl-4(3*H*)-quinazolinone Derivatives

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Some 2-(fluoromethyl) analogues of 2-methyl-3-aryl-4(3*H*)-quinazolinones have been synthesized and screened for CNS activities. It was shown that the 2-(fluoromethyl) analogues possess in general more potent CNS depressant activities and less toxicities than their parent compounds. Of particular interest were the 2-(fluoromethyl) analogues (**22**, **24**, and **31**) of methaqualone and 6-aminomethaqualone. Compound **24** was more potent in CNS depressant activity and less toxic than methaqualone. Compound **31** exhibited potent central muscle relaxing activity and markedly reduced toxicity as compared with 6-aminomethaqualone.

Numerous synthetic efforts on halogen-containing compounds have been made to exploit the pharmacophoric effect of halogenation. The most fruitful success has been achieved by the introduction of a fluorine atom into an already active compound, resulting in the following beneficial changes in molecular properties: (1) higher fat solubility giving different absorption and transport rate; (2) altered electronic effects; (3) improved stability; (4) equivalent steric size.

In recent years we have investigated the synthesis[1] and biological activity of 2,3-dihydro-4(1*H*)-quinazolinone derivatives and their related compounds in order to develop potent analgesics. During these studies it was found incidentally that some 1-(*tert*-aminoacetyl)-2-methyl-3-phenyl-2,3-dihydro-4(1*H*)-quinazolinones possessed strong choleretic activity.[1c] The highest activity was exhibited with 1-(morpholinoacetyl)-2-methyl-3-phenyl-2,3-dihydro-4(1*H*)-quinazolinone. From a study of the structure–activity relationship, it has been found that the introduction of a substituent into the fused benzene ring generally reduced the activity. Elongation of the alkyl chain at C-2 also resulted in a significant decrease in activity and an increase in toxicity. However, the 2-(fluoromethyl) analogue showed equipotent activity, suggesting an important role of steric size at C-2 for the activity. This is in accord with an earlier observation[2a] on the steric requirement at C-2 of 2-methyl-3-(*o*-tolyl)-4-(3*H*)-quinazolinone (methaqualone) for hypnotic activity. In view of these results it became of interest to synthesize 2-(fluoromethyl) analogues of 2-methyl-3-aryl-4(3*H*)-quinazolinone derivatives in an attempt to prepare improved neurotropic drugs. We describe here our findings in the synthesis of some 2-(fluoromethyl)-3-aryl-4(3*H*)-quinazolinones and their pharmacological activities.

The structural modifications[2] of methaqualone reported to date involve mainly the additional substitution with various functional groups on the 3-tolyl moiety and/or on the fused benzene ring and the replacement of the 2-methyl group with longer alkyl groups. After our preliminary communication[3] on the hypnotic activity of 2-(fluoromethyl)-3-(*o*-tolyl)-4(3*H*)-quinazolinone (**22**) appeared, a number of new derivatives bearing halogen, amino, alkoxy, and sulfide groups on the 2-methyl group were reported by Taylor[4] and his co-workers.

Chemistry. The 2-(fluoromethyl)-3-aryl-4(3*H*)-quinazolinones IV were prepared as shown in Scheme I via three steps from the corresponding anthranilic acids. A fusion reaction of anilines with isatoic anhydride is well-known as a general method[5] for the preparation of anthranilanilides. However, this method requires handling of phosgene in the preparation of isatoic anhydride. In order to avoid the hazards with phosgene, we attempted the alternate reaction of anthranilic acids I with thionyl chloride in boiling benzene, followed by treatment with

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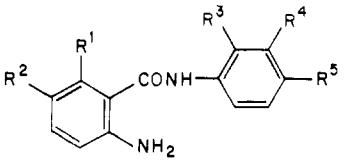
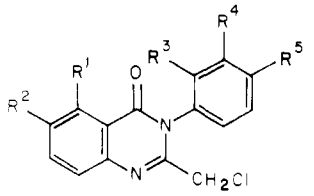
Table I. 2-Aminobenzanilides II



compd no.	R^1	R^2	R^3	R^4	R^5	yield, %	mp, °C	recrystn solvent[f]	analyses
1	H	H	H	H	H	63.7	131-133[a]		
2	H	H	CH_3	H	H	71.4	108-110[b]		
3	H	H	CH_3	H	Cl	56.6	144-148[c]	A	C, H, N
4	H	H	CH_3	Cl	H	35.8	126-127	A	C, H, N
5	H	H	Cl	H	Cl	24.1	102-104	A	C, H, N
6	Cl	H	CH_3	H	H	66.2	107-108	A	C, H, N
7	Cl	H	CH_3	H	Cl	43.4	145-147	B	C, H, N
8	H	Cl	CH_3	H	H	40.8	176-177[d]	B	C, H, N
9	H	NO_2	CH_3	H	H	79.5	209-212	B	C, H, N
10	H	NHAc	CH_3	H	H	86.4[e]	219-221	C	C, H, N

[a] Lit. mp 128.5-129 °C: J. R. Feldmann and E. C. Wagner, *J. Org. Chem.*, **7**, 31 (1942). [b] Lit. mp 104-105 °C: P. A. Petyunin and Yu. V. Kozhevnikov, *Zh. Obshch. Khim.*, **30**, 2028 (1960). [c] Lit. mp 130-136 °C: *Chem. Abstr.*, 69, 52188m (1968). [d] Lit. mp 151-152 °C: P. A. Petyunin and Yu. V. Kozhevnikov, *Biol. Akt. Soedin.*, *1965*, 152 (1965). [e] Prepared by reduction of 9, followed by acetylation. [f] A = diisopropyl ether, B = EtOH, C = MeOH-H_2O.

Table II. 2-(Chloromethyl)-3-aryl-4(3*H*)-quinazolinones III



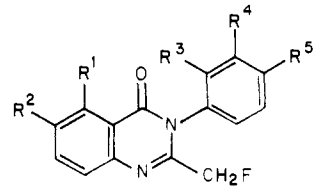
compd no.	R^1	R^2	R^3	R^4	R^5	yield, %	mp, °C	recrystn solvent[e]	analyses
11	H	H	H	H	H	61.1	152-154[a]		
12	H	H	CH_3	H	H	73.8	103-105[b]		
13	H	H	CH_3	H	Cl	90.0	124-127	A	C, H, N
14	H	H	CH_3	Cl	H	92.8	149-152	A	C, H, N
15	H	H	Cl	H	Cl	94.4	134-137	A	C, H, N
16	Cl	H	CH_3	H	H	54.9	164-166	A	C, H, N
17	Cl	H	CH_3	H	Cl	55.6	188-190[d]		
18	H	Cl	CH_3	H	H	85.1	204-206[c]		
19	H	NO_2	CH_3	H	H	90.4	187-190	A	C, H, N
20	H	NHAc	CH_3	H	H	81.4	219-221	A	C, H, N

[a] Lit.[2c] mp 151-152 °C. [b] Lit.[2c] mp 115-116 °C. [c] Lit.[2c] mp 201-204 °C. [d] Lit. mp 183-185 °C: H. Yamamoto, S. Inaba, M. Nakao, and I. Maruyama, *Chem. Pharm. Bull.*, 17, 400 (1969). [e] A = EtOH.

the anilines. This procedure afforded the anthranilanilides II in moderate yields in most cases, while in the case of the aniline substituted with an electron-withdrawing group the yield dropped sharply because of the weakened nucleophilicity of the amino group (Table I). No effort was made to isolate the intermediates formed in the first step of this procedure. However, in the reaction of 5-nitroanthranilic acid with thionyl chloride, an intermediate could be isolated by chance as fine yellow needles. Its structure was assigned 2-amino-5-nitrobenzoyl chloride on the basis of elemental analysis and IR spectrum. It should be noted that in the case of anthranilic acid different products [*o*-(thionylamino)benzoyl chloride[6] and 3,2,1-benzoxathiazin-4-(1*H*)-one 2-oxide[7]] have been obtained independently by two groups of workers. It is difficult to explain this inconsistency. However, a possible reason would be the difference of the reaction conditions. In any event the amino group of anthranilic acids may be considered generally to be susceptible to the reaction with thionyl chloride. The unexpected behavior of the amino group of 5-nitroanthranilic acid would be attributable to the strong electron withdrawal by both nitro and carboxyl groups.

The 2-(chloromethyl)-3-aryl-4(3*H*)-quinazolinones III were prepared via chloroacetylation of the anthranilanilides II with excess chloroacetyl chloride in acetic acid, followed by spontaneous cyclization at 110 °C according to Petyunin's procedure[2c] (Table II). The cyclization seems to be accelerated with the hydrogen chloride generated in situ, since when the isolated (chloroacetyl)-anthranilanilides were heated in acetic acid the cyclization was sluggish to give the quinazolones III in low yields. The chlorine atom at the 2-methyl group of the quinazolones III could be readily displaced by the fluorine atom. Thus, the quinazolones III were treated with anhydrous potassium fluoride (3 molar ratio) at 160 °C in ethylene glycol for 2–4 h to give the 2-(fluoromethyl)quinazolones IV in good yields (Table III). A small amount of 2-[[(β-hydroxyethyl)oxy]methyl]-3-aryl-4(3*H*)-quinazolinone was usually formed as a by-product, its formation being suppressed by minimizing the amount of ethylene glycol.[8] The fluorine exchange reaction of 2-(chloromethyl)-6-nitro-3-(*o*-tolyl)-4(3*H*)-quinazolinone (**19**) under the same condition afforded the corresponding 2-(fluoromethyl)-quinazolone **29** in very low yield. Alternatively, the reaction using KHF_2 (5 molar ratio) in diethylene glycol

Table III. 2-(Fluoromethyl)-3-aryl-4(3*H*)-quinazolinones IV



compd no.	R¹	R²	R³	R⁴	R⁵	yield, %	mp, °C	recrystn solvent[b]	analyses
21	H	H	H	H	H	69.2	101-103	A	C, H, N
22	H	H	CH_3	H	H	47.0	103-105	A	C, H, N
23	H	H	CH_3	H	Cl	72.7	124-125	B	C, H, N
24	H	H	CH_3	Cl	H	76.6	163-165	C	C, H, N
25	H	H	Cl	H	Cl	65.1	133-134	B	C, H, N
26	Cl	H	CH_3	H	H	60.0	154-156	B	C, H, N
27	Cl	H	CH_3	H	Cl	35.6	140-142	B	C, H, N
28	H	Cl	CH_3	H	H	55.0	154-155	B	C, H, N
29	H	NO_2	CH_3	H	H	67.3	156-158	C	C, H, N
30	H	NHAc	CH_3	H	H	70.0	239-242	C	C, H, N
31	H	NH_2	CH_3	H	H	61.7[a]	194-196	B	C, H, N

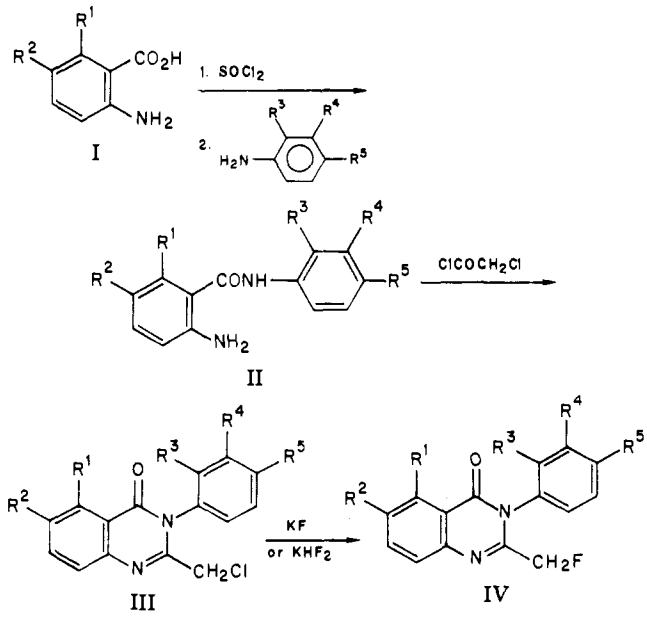
[a] Prepared by deacetylation of compound 30. [b] A = diisopropyl ether, B = 2-propanol, C = EtOH.

Table IV. Pharmacological Data. ED_{50} Values in the Mouse

compd no.	LD_{50}, mg/kg ip (95% CL)[a]	ED_{50}, mg/kg ip (95% CL)			
		LRR[c]	RR[d]	MES[e]	PTZ[f]
21	⩾300[b]	130.3 (113.8-153.1)	98.0 (89.9-109.4)	116.4 (109.1-127.4)	95.3 (88.6-114.8)
22	710.0 (556.5-888.2)	19.9 (15.8-25.7)	35.1 (27.1-45.6)	25.2 (18.4-34.2)	26.6 (17.6-42.0)
23	432.1 (334.4-558.4)	18.7[g] (14.9-22.5)	not tested	14.1 (11.2-17.6)	16.3 (13.5-20.4)
24	1562.1 (1280.6-1905.4)	18.4 (14.4-24.2)	15.0 (12.1-18.7)	15.0 (12.1-18.7)	16.1 (11.9-21.2)
25	100[b]	18.7[g] (14.9-22.5)	not tested	8.1 (6.8-9.5)	16.3 (13.5-20.4)
26	⩾300[b]	95.7 (88.4-115.9)	37.6 (28.3-49.7)	40.3 (27.2-57.4)	34.9 (28.1-43.1)
27	⩾300[b]	>150	>150	>150	88.4 (81.6-97.9)
28	⩾300[b]	>150	>150	>150	>150
29	⩾300[b]	>150	>150	>150	>150
30	⩾300[b]	>150	>150	>150	75.2 (69.1-83.3)
31	315.1 (265.5-373.8)	35.1 (28.7-43.0)	15.6 (12.1-20.2)	13.3 (11.1-15.7)	5.4 (4.1-7.2)
methaqualone	542.1 (456.9-643.5)	31.6 (25.7-39.8)	33.7 (26.7-42.7)	35.2 (29.1-42.9)	36.7 (29.8-44.9)
6-amino-methaqualone	95.9 (79.1-116.5)	28.1 (22.4-34.8)	27.9 (23.4-33.1)	25.4 (21.6-29.9)	8.1 (3.9-16.6)

[a] Confidence limits for $p = 95\%$. [b] Maximal tolerated dose, mg/kg ip. [c] Loss of righting reflex test. [d] Rotating rod test. [e] Maximal electroshock test. [f] Pentylenetetrazole test. [g] Excitation was observed at this dose.

Scheme I



under a similar condition gave an improved yield (55%). The best yield (67%) was obtained when CsF was employed as a fluorinating agent. 6-Amino-2-(fluoromethyl)-3-(*o*-tolyl)-4(3*H*)-quinazolinone (**31**) could be prepared in good yield by the reaction of **29** with stannous chloride or by the acidic deacetylation of **30**.

Pharmacology and Discussion. The CNS activities of compounds **21**–**31** studied on the several pharmacological parameters are shown in Table IV, and those of methaqualone and 6-aminomethaqualone are included for comparison.

Most of the compounds prepared in this study exhibited CNS depressant activity. In general, the 2-(fluoromethyl) analogues possess similar pharmacological properties to those of the corresponding 2-methyl derivatives. Of particular interest are a marked decrease in the toxicity of **31** and an increase in CNS depressant activity of some fluorinated compounds such as **22**, **24**, and **31** as compared with each parent compound.[9] In the early study[3] some of the authors showed that the 2-(fluoromethyl) analogue **22** had more potent hypnotic activity than methaqualone, and the ratio LD_{50}/ED_{50} in the righting reflex test of the former was larger than that of the latter. A similar pharmacological profile with **22** has been reported by Taylor.[4]

Boltze and co-workers[2a] have studied the pharmacological activities of methaqualone derivatives and found that introduction of a chlorine atom into the meta position of the 3-phenyl group of methaqualone caused a reduction in acute toxicity and a potentiation of hypnotic activity,

whereas introduction of a chlorine atom into the para position resulted in an enhancement of both acute toxicity and hypnotic activity followed by marked excitation. These structure–activity relationships were also recognized partly in the 2-(fluoromethyl) analogues IV. The meta-chlorinated compound **24** showed much less toxicity than **22**, whereas the para-chlorinated compound **23** exhibited rather enhanced toxicity. Thus, the ratio LD_{50}/ED_{50} in the righting reflex test of compound **24** was much more improved than that of compound **22**, suggesting that compound **24** might serve as a more potent hypnotic with lower toxicity than not only methaqualone but also compound **22**. In the case of **23**, a marked excitation was also observed as in the methaqualone series. Unlike the methaqualone derivatives, however, both **23** and **24** showed an almost identical activity in the righting reflex test. The introduction of a chlorine atom on the fused benzene ring of methaqualone has been reported[2a] to cause a marked decrease in the hypnotic activity. The same pharmacological trend was observed with the 2-(fluoromethyl) analogue **28**. It has been found by Takagi[2d] that 5-chloro-3-(4-chloro-2-methylphenyl)-2-methyl-4(3*H*)-quinazolinone possesses a tranquilizing action similar to that of chlordiazepoxide. The corresponding 2-(fluoromethyl) analogue **27**, however, exhibited only a weak anti-pentylenetetrazole activity.

Breuer and Roesh[2f] discovered that introduction of an amino group into the 6 position of methaqualone brought about marked central muscle relaxant activity. The corresponding 2-(fluoromethyl) analogue **31** exhibited an almost equal pharmacological profile to that of 6-aminomethaqualone. The ED_{50} values of **31** in the rotating rod and the maximal electroshock tests were significantly smaller than those of 6-aminomethaqualone. Therefore, the ratio (ED_{50} in the righting reflex test)/(ED_{50} in the rotating rod test) of the compound **31** was improved as compared with that of the parent compound. Recently, some of the authors have confirmed that the muscle relaxant activity of **31** is derived from the suppression of polysynapses in the spinal cord.[10] These results and a dramatic decrease in acute toxicity observed suggest that compound **31** might serve as a more useful muscle relaxant than 6-aminomethaqualone. Hereupon, though acute toxicity of compound **24** was much weaker than that of **31**, ED_{50} values of **24** in the righting reflex and rotating rod tests were so close that **24** should be considered as a hypnotic rather than a muscle relaxant.

In conclusion, it was shown that the introduction of a fluorine atom into the 2-methyl group of 2-methyl-3-aryl-4(3*H*)-quinazolinones is an effective approach for exploiting the pharmacophoric effect of halogenation.

Experimental Section

Chemistry. All melting points are uncorrected. Mass spectra were recorded on a Hitachi RMS-4 spectrometer and infrared spectra on a Shimadzu IR-27G.

General Procedure for Preparation of 2-Aminobenzanilides II. Typical Procedure: 2-Amino-5-nitrobenzo-*o*-toluidide (9). A mixture of 5-nitroanthranilic acid (20.0 g, 0.109 mol), $SOCl_2$ (50 g, 0.42 mol), and benzene (200 mL) was refluxed for 5 h. The excess $SOCl_2$ and the solvent were removed by evaporation. The yellow crystalline residue was dissolved in $CHCl_3$ (200 mL) and then treated with *o*-toluidine (35.1 g, 0.327 mol). The mixture was refluxed for 2 h, and the crystals which had formed were collected by filtration, washed with $CHCl_3$, with 5% aqueous NaOH, and with H_2O, and then dried to give 22.3 g (75%) of almost pure **9**, mp 209–212 °C. Anal. ($C_{14}H_{13}N_3O_3$) C, H, N. A further crop (1.3 g, 4.5%) was obtained from the $CHCl_3$ filtrate.

Isolation of Intermediate: 2-Amino-5-nitrobenzoyl Chloride. The yellow crystals which were obtained from the reaction mixture of 5-nitroanthranilic acid with $SOCl_2$ could be purified by recrystallization from benzene to afford bright yellow needles: mp 156–159 °C dec; ν_{max}^{Nujol} 3460, 3350, 1720, 1620, 1600 cm^{-1}; mass spectrum *m/e* 202 ($M^+ + 2$), 200 (M^+), 165, 119, 91. Anal. Calcd for $C_7H_3ClN_2O_3$: C, 41.91; H, 2.51; N, 13.97; Cl, 17.68. Found: C, 42.25; H, 2.61; N, 14.18; Cl, 17.41.

General Procedure for Preparation of 2-(Chloromethyl)-3-aryl-4(3*H*)-quinazolinones III. Typical Procedure: 2-(Chloromethyl)-3-(4-chloro-2-methylphenyl)-4(3*H*)-quinazolinone (13). To a suspension of 2-aminobenzo-4′-chloro-2′-methylanilide (3, 3.0 g, 0.0115 mol) in AcOH (30 mL) was added dropwise chloroacetyl chloride (3.9 g, 0.035 mol) at room temperature, and then the mixture was heated at 110 °C for 2 h. After cooling, the reaction mixture was concentrated in vacuo to dryness. The residual crystals were dissolved in H_2O and neutralized with K_2CO_3. The oily product was extracted with benzene and the benzene layer was dried with anhydrous K_2CO_3. Evaporation of the solvent followed by trituration of the residue with 2-propanol gave crude crystalline **13**, which upon recrystallization from 2-propanol afforded 3.3 g (90%) of pure **13**, mp 124–127 °C. Anal. ($C_{16}H_{12}Cl_2N_2O$) C, H, N.

General Procedure for Preparation of 3-Aryl-2-(fluoromethyl)-4(3*H*)-quinazolinones IV. Typical Procedure: (a) 2-(Fluoromethyl)-3-(*o*-tolyl)-4(3*H*)-quinazolinone (22). A mixture of 2-(chloromethyl)-3-(*o*-tolyl)-4(3*H*)-quinazolinone (20.0 g, 0.075 mol), anhydrous KF (13.0 g, 0.225 mol), and ethylene glycol (14 mL) was heated at 160–170 °C (bath temperature) for 2 h. After cooling, the mixture was poured into H_2O and extracted with benzene. The benzene layer was dried with anhydrous $MgSO_4$ and then concentrated to an oil, which was crystallized by trituration with 2-propanol (40 mL) to give crude, crystalline **22** (12.6 g). Recrystallization from 2-propanol gave pure **22** (11.0 g, 57.7%), mp 101–103 °C. Anal. ($C_{16}H_{13}FN_2O$) C, H, N. Further crops (2.2 g, 11.5%) were obtained by purification of the crude product which was recovered from the mother liquors in the crystallization.

(b) 2-(Fluoromethyl)-6-nitro-3-(*o*-tolyl)-4(3*H*)-quinazolinone (29). A mixture of **19** (3.29 g, 0.01 mol), CsF (4.51 g, 0.03 mol), and diethylene glycol (20 mL) was heated at 130 °C for 50 min. After cooling, the mixture was poured into H_2O and extracted with $CHCl_3$. The chloroform layer was dried with anhydrous $MgSO_4$. Evaporation of the solvent, followed by column chromatography using silica gel (solvent, $CHCl_3$), gave pure **29** (2.1 g, 67.3%), mp 155–157 °C. Anal. ($C_{16}H_{12}FN_3O_3$) C, H, N.

2-Amino-5-(acetylamino)benzo-*o*-toluidide (10). A suspension of **9** (54.4 g, 0.2 mol) and 5% Pd on charcoal (6.0 g) in MeOH (1 L) was shaken in an atmosphere of hydrogen (initial pressure of 50 lb) at 40–50 °C. After cessation of hydrogen uptake, the catalyst was removed by filtration and the filtrate was cooled to 0–5 °C. A solution of acetic anhydride (20.4 g, 0.2 mol) in benzene (500 mL) was added dropwise to the hydrogenated solution for 3 h. The reaction mixture was stirred at room temperature for 1 h and then concentrated to dryness in vacuo. The residual crystals were triturated with 2-propanol and collected by filtration to give pure **10** (49.0 g, 86.4%), mp 215–217 °C. Anal. ($C_{16}H_{17}N_3O_2$) C, H, N.

6-Amino-2-(fluoromethyl)-3-(*o*-tolyl)-4(3*H*)-quinazolinone (31). A solution of **30** (10.0 g) in 10% HCl–MeOH (250 mL) was allowed to stand at room temperature for 3 h. After evaporation of the solvent, the residue was dissolved in cold H_2O and neutralized with $NaHCO_3$. The oily product was extracted with $CHCl_3$, and the chloroform layer was dried with anhydrous $MgSO_4$. Evaporation of the solvent followed by trituration with 2-propanol gave **31** (5.4 g, 61.7%) as pale yellow prisms, mp 194–196 °C. Anal. ($C_{16}H_{14}FN_3O$) C, H, N.

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 six mice in increasing doses. The animals were observed for 72 h and the lethality after that time was used for determining the LD_{50} value.

Righting Reflex Test. Groups of six mice were injected intraperitoneally with the test compounds. After 15, 30, 60, 90, and 120 min each animal was placed gently on its back on the desk. When the animal remained on its back over 20 s, the reflex was considered lost. The ED_{50} value was estimated from the

number of mice which lost the reflex over 20 s.

Rotating Rod Test. Groups of six 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.

Maximal Electroshock Test. Groups of six mice were injected intraperitoneally with the test compounds. After 30 min the alternating current of 25 mA was delivered for 0.15 s through corneal electrodes. The ED_{50} value was estimated from the number of mice which were protected against the tonic extensor component of the hind limbs.

Pentylenetetrazole Convulsions. Groups of six mice were injected intraperitoneally with the test compounds. After 30 min pentylenetetrazole was injected subcutaneously at a dose of 125 mg/kg. The ED_{50} value was estimated from the number of mice which were protected against death due to tonic extensive convulsions within 1 h after administration of the convulsant.

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(9) The direct comparison of **24** with its parent compound in the CNS depressant activity was not made. However, the higher activity of **24** is supportedly shown by the values reported in the ref 2a.

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Kojic Amine—a Novel γ-Aminobutyric Acid Analogue

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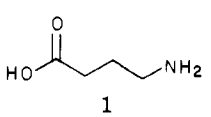
A series of compounds containing the 3-hydroxy-4*H*-pyran-4-one nucleus has been synthesized and tested as potential skeletal muscle relaxants. Reduction of 2-(azidomethyl)-5-hydroxy-4*H*-pyran-4-one (**4**) with HBr in HOAc–phenol yielded 2-(aminomethyl)-5-hydroxy-4*H*-pyran-4-one (kojic amine, **3**) in 81% yield. Reaction of 2-[(tosyloxy)-methyl]-5-(benzyloxy)-4*H*-pyran-4-one (**5**) with NH_3 gave a 40% yield of the *O*-benzyl ether of kojic amine, which was N-acylated with a series of carbobenzyloxy-protected amino acids. Complete deprotection with HBr–HOAc gave the following amino acid amides of kojic amine: glycyl (**23**), α-alanyl (**24**), β-alanyl (**25**), γ-aminobutyryl (**26**), and glycylglycyl (**27**). Among the analogues of kojic amine prepared was a series of one-carbon homologues: 2-[(methylamino)methyl]-5-hydroxy-4*H*-pyran-4-one (**7a**), 2-(1-aminoethyl)-5-hydroxy-4*H*-pyran-4-one (**8**), 6-(aminomethyl)-3-hydroxy-2-methyl-4*H*-pyran-4-one (**12**), and 2-(2-aminoethyl)-5-hydroxy-4*H*-pyran-4-one (**16**). Kojic amine (**3**) has been found to possess certain of the properties to be expected in a γ-aminobutyric acid mimetic agent, notably skeletal muscle relaxant activity. In the chronic spinal cat preparation, ED_{70} values for reduction of flexor spasms of 2.2 and 4.0 mg/kg by iv and po routes of administration, respectively, were observed for kojic amine, which was the most potent of the various hydroxypyrone derivatives investigated.

γ-Aminobutyric acid (GABA, **1**) is believed to play a



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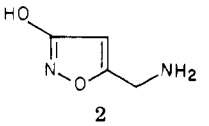

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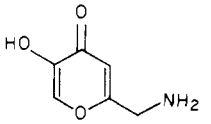

3

major role in vertebrates as an inhibitory neurotransmitter, both at the brain and spinal levels.[1,2] As GABA itself does not cross the blood–brain barrier, there is considerable interest in the development of systemically active GABA-mimetic agents. These agents might have therapeutic utility in neurological disorders such as Huntingdon's chorea,[3] schizophrenia,[4] and epilepsy,[5] as well as in analgesia[6] and in the treatment of skeletal muscle spasticity. Muscimol (**2**), a potent, orally active, naturally occurring GABA-like agent, is toxic and has been reported to cause hallucinations in man.[7] The very recent report[8] that muscimol is a potent blood pressure lowering agent when administered intracerebroventricularly indicates a possible involvement of GABA receptors in the central regulation of blood pressure. The structure of muscimol, which corresponds to the extended conformation of

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