Methyl α-Bromo-*o*-nitrophenylacetate (5). A mixture of 20 g (0.09 mol) of methyl *o*-nitromandelate and 75 g (0.3 mol) of PBr_3 was stirred at 25° for 2 hr. The excess PBr_3 was removed from the reaction mixture with a current of air, and the residual oil was dissolved in a small amount of EtOH. Cooling of the solution gave a precipitate which was filtered to yield 17 g (65%) of product. An analytical sample was obtained by recrystallization from EtOH, mp 61–62°. *Anal.* ($C_9H_8NO_4Br$) C, H, N.

Methyl α-Phthalimido-*o*-nitrophenylacetate (6). A mixture of 11.2 g (0.05 mol) of **5** and 8.5 g (0.05 mol) of potassium phthalimide in 170 ml of DMF was stirred at 25° for 2 hr. The KBr was removed by filtration, and the filtrate was treated with 200 ml of $CHCl_3$ and 500 ml of H_2O. The $CHCl_3$ layer was separated and the aqueous layer was extracted twice with 200-ml portions of $CHCl_3$. The $CHCl_3$ extracts were combined, dried over anhydrous Na_2SO_4, and taken to dryness *in vacuo* to give a dark-colored oil. Treatment of the oil with hot EtOH effected the separation of a white solid. The precipitate was filtered, washed with H_2O, and dried *in vacuo* to yield 10.1 g (72%) of product. An analytical sample was obtained by recrystallization from EtOH, mp 151–152°. *Anal.* ($C_{17}H_{12}N_2O_6$) C, H, N.

***o*-Nitrophenylglycine (7).** A solution of 10.0 g (0.03 mol) of **6** in 20 ml of glacial AcOH and 30 ml of concentrated HCl was heated under reflux for 5 hr. The phthalic acid was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was treated with a few milliliters of H_2O and the solution was adjusted to pH 7 with addition of concentrated NH_4OH. Evaporation of the solution gave an oily residue from which a solid formed on treatment with EtOH. The precipitate was filtered and washed with H_2O to give 2.2 g (38%) of product, mp 142–143°. *Anal.* ($C_8H_8N_2O_4$) C, H, N.

In a separate experiment, 18.5 g (0.05 mol) of **6** was hydrolyzed in 100 ml of refluxing concentrated HCl–AcOH (6:4) for 5 hr. After removal of the phthalic acid by filtration from the cooled reaction mixture, the filtrate was taken to dryness *in vacuo*. The resulting solid residue was recrystallized from MeOH–Et_2O to yield 10.45 g (83%) of *o*-nitrophenylglycine hydrochloride, mp 116–118° dec. This compound was used without further purification for the synthesis of **2**.

3-Amino-1-hydroxy-2-indolinone Hydrochloride (2). To 1.0 g (0.004 mol) of the HCl salt of **7** dissolved in 6 ml of 50% aqueous CH_3OH was added 1 ml of concentrated HCl and reduced at 3.18 kg/cm² H_2 pressure in the presence of 20 mg of 5% Pt on C for 30 min. The catalyst was removed by filtration and the filtrate was taken to dryness *in vacuo*. The residue was dissolved in a minimum amount of hot CH_3OH and treated with 2 vol of Et_2O. Chilling of the solution at −17° gave 0.54 g (62%) of product, mp 210–211° dec (turns pink at 165° and darkens at 200°). This compound gives a deep blue with $FeCl_3$ reagent. *Anal.* ($C_8H_8N_2O_2$·HCl) C, H, N.

***o*-Aminophenylglycine (8).** **7** (1 g, 0.006 mol) dissolved in 100 ml of H_2O was reduced at 3.18 kg/cm² H_2 pressure in the presence of 300 mg of Pd black for 12 hr. The catalyst was removed by filtration, and the filtrate was concentrated in volume *in vacuo*. Treatment of the concentrated solution with EtOH caused precipitation. Filtration gave 0.52 g (61%) of product, mp 204–205°. *Anal.* ($C_8H_{10}N_2O_2$) C, H, N.

3-Amino-2-indolinone Hydrochloride (4). To a 100-mg (0.0006 mol) sample of **7** in 10 ml of 75% aqueous MeOH was added 0.5 ml of concentrated HCl. After 1 hr the solution was taken to dryness *in vacuo*. The residue was recrystallized from CH_3OH–Et_2O. After filtration the precipitate was dried *in vacuo* to give 108 mg (97%) of product, mp 210–215° dec (turns pink at 175°, red at 200°; lit. mp 175° *via* different procedure[6]). *Anal.* ($C_8H_8N_2O$·HCl) C, H, N.

Microbiological Assays. For the assays with *L. dextranicum* (ATCC 8086) a previously described assay procedure and basal medium[7] were used except that histidine, phenylalanine, and tyrosine were omitted; 0.2 μg/ml of calcium pantothenate and 0.02 μg/ml of pantethine were added; and the phosphate (salts A) concentration was increased fourfold. The assay procedure[8] and the inorganic salts–glucose medium[9] for *E. coli* (ATCC 9723) were the same as those previously described. In all assays the amount of growth was determined spectrophotometrically at 625 mμ with a Bausch and Lomb Spectronic 20 spectrophotometer in terms of absorbance readings of the turbid culture medium against a blank of uninoculated medium set at 0 absorbance.

The compounds (10 mg) were dissolved in sterile H_2O (10 ml) at 25°. From these solutions, serial dilutions were made and added aseptically to the previously autoclaved assay tubes without heating. After inoculation, the assay tubes with *L. dextranicum* were incubated at 30° for 24 hr, and those with *E. coli* were incubated at 37° for 16 hr. For each assay, appropriate controls were performed and reproducible results of the minimum inhibitory concentrations of compounds were obtained on repeating the assay 12 times.

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Synthesis and Central Nervous System Depressant Activity of Some 2-Aryl-6-chloro-4-phenylquinazolines

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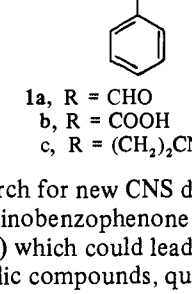
Six out of the seven 1,4-benzodiazepine type drugs introduced for clinical use as tranquilizers or sleep inducers bear two particular common structural features.[1] These features are the 5-phenyl and 7-chloro substituents. From a synthetic point of view, these six drugs may be conceived of as derived from 5-chloro-2-aminobenzophenone.

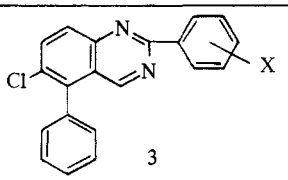
The structural moiety corresponding to 5-chloro-2-aminobenzophenone is also observed in other centrally acting nitrogen heterocyclic compounds. For example, the quinazolines **1a** and **1b** (R = CHO, CO_2H) are useful muscle relaxants,[2] while **1c** is useful as an anticonvulsant.[3] Consequently, in our search for new CNS depressants, we have used 5-chloro-2-aminobenzophenone hydrazone (**2**) in a reaction (Scheme I) which could lead theoretically to two types of heterocyclic compounds, quinazolines or benzotriazepines.



1a, R = CHO
b, R = COOH
c, R = $(CH_2)_2CN$

Chemistry. When 5-chloro-2-aminobenzophenone hydrazone (**2**) was treated with different aryl imido ester hydrochlorides, the only crystalline products obtained were the corresponding new 2-aryl-6-chloro-4-phenylquinazolines (**3a–g**, Table I). No benzotriazepine (**4**) was formed. To our knowledge, this is the first report of the use of this reaction

Table I. 2-Aryl-6-chloro-4-phenylquinazolines



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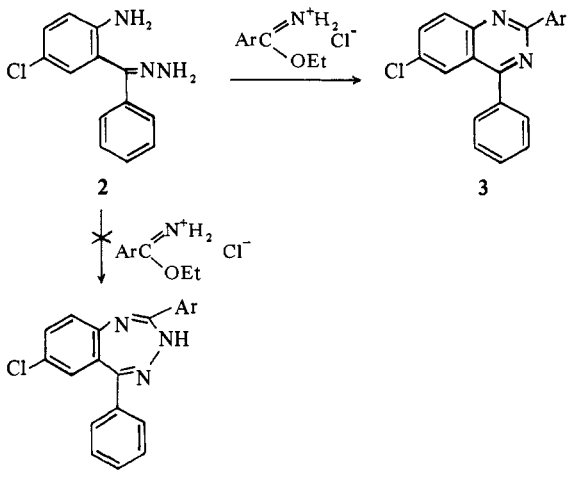
Compd	X	Mp,[a] °C	Yield, %	Formula[b]	LD_{50},[c] mg/kg ip	Behavioral screening[c,d] (CNS depressant activity at mg/kg ip)	Potentiation of hexobarbital ($ED_{+300\%}$, mg/kg ip)
3a	4-Cl	202–205	28	$C_{20}H_{12}Cl_2N_2$	≫1000	– at 400	90
3b	4-OH	285	32	$C_{20}H_{13}ClN_2O$	≫1000	++ at 120	400
3c	3-O-C_6H_4(4-NO_2)	215	30	$C_{26}H_{16}ClN_3O_3$	≫1000	++ at 120	380
3d	3-NO_2	186–188	26	$C_{20}H_{12}ClN_3O_2$	≫1000	++ at 120	>400
3e	3-F	202	28	$C_{20}H_{12}ClFN_2$	≫1000	++ at 40	>400
3f	3,5-(NO_2)$_2$	230	34	$C_{20}H_{11}ClN_4O_2$	≫1000	++ at 120	>400
3g	3-CF_3	160	36	$C_{21}H_{12}ClF_3N_2$	≫1000	– at 400	>400
Chlordiazepoxide					390	++++ at 6	22
Diazepam					560	++++ at 3	3.6

[a] All compounds were recrystallized from *n*-BuOH–DMF. [b] All compounds were analyzed for C, H, and N and the results obtained were within ±0.4% of calculated values. [c] For description of biological procedures and reference citations, refer to the Experimental Section [d] Rating of CNS depressant activity: –, nil; +, very mild; ++, mild; +++ good; ++++, very good.

Scheme I



2 3 4

for the preparation of quinazolines of the structure described. Some 2-aryl- and 2-alkyl-6-substituted 4-phenylquinazolines are known,[4-8] but synthetic routes other than the one described here have been used for their preparation.

Pharmacology. Compounds **3a–g** were submitted to a battery of behavioral and drug interaction tests[9-16] in mice to evaluate their potential as CNS depressants, using chlordiazepoxide and diazepam as reference compounds. All compounds were administered intraperitoneally as a 1% carboxymethylcellulose suspension, except in the methamphetamine-mouse test in which the suspension was administered *per os*.

As can be seen from Table I, in which only the most interesting results are reported, compounds **3b–f** caused CNS depression, as measured by a series of parameters including mild sedation, reduction in activity, relaxation of the muscle tonus, and diminution of the holding reflex. Compound **3e** also produced a temporary reduction of the reaction to an acoustic impulse. Compounds **3a–c** potentiated hexobarbital-induced sleep. None of the compounds at doses of 400 mg/kg showed any anticonvulsant action against maximal electroshock (MES) seizures,[13] taming effect of Syrian hamsters,[14] reduction in the exploration and motility of a methamphetamine mouse,[15] and stimulation of apomorphine-induced gnawing.[16]

Conclusions

All the quinazolines described exhibited some mild CNS depressant properties. Variations in the 2-aryl substituent did not reveal any special structure-activity correlations. In comparison with the standard drugs, chlordiazepoxide and diazepam, the compounds had an uninteresting biological profile and were active only at relatively high doses.

Experimental Section

The ir spectra were recorded on a Perkin-Elmer spectrophotometer, Model 521 in KBr; the nmr spectra were obtained on a Varian A-60 and T-60 spectrometer (Me_4Si). The mass spectra were recorded on a MS 9 (AEI). The melting points were determined on a Kofler heating bench, Type 7841. Ir, nmr, and mass spectra were consistent with the structures assigned.

2-Substituted 6-Chloro-4-phenylquinazolines (3a–g). 5-Chloro-2-aminobenzophenone hydrazone (0.05 mol) was dissolved in 150 ml of DMF and 0.08 mol of the corresponding imido ester hydrochloride was added. After refluxing for 3–4 hr, the solvent was distilled *in vacuo* and the residue washed three times with H_2O at 50°. The aqueous layer was decanted and the solid material was crystallized from *n*-BuOH–DMF (Table I).

Pharmacology. Actue Toxicity. Six mice (18–22 g, Kasauli strain) were used for each of two doses, 300 and 1000 mg/kg. The test compound was administered ip as a 1% carboxymethylcellulose suspension. All mice were observed for 72 hr. LD_{50} was calculated according to the method of Litchfield and Wilcoxon.[9]

Behavioral Screening. The procedure, equipment, and physical arrangement according to the method of Irwin[10] were used with minor modifications as follows. Three test groups, each composed of four mice (18–22 g, Kasauli strain), were treated such that in each group one animal received only solvent and the remaining three received three different doses of the test compound, *viz.* 400, 120, and 40 mg/kg. All the compounds were administered ip as a 1% carboxymethylcellulose suspension. The test compounds and the standard drugs were rated according to the scale indicated in Table I using as criteria their effect on spontaneous behavior, locomotor activity, response to stimulation, and appearance.

Hexobarbital Narcosis Potentiation.[11,12] Kasauli mice (18–22 g) were treated ip with sublethal doses of a 1% carboxymethylcellulose suspension of the test compound followed in 1 hr by an iv administration of 55 mg/kg of hexobarbital. Six mice were used at each dose level, *viz.* 400, 200, 100, and 50 mg/kg. The sleeping time was measured as the interval between the administration of hexobarbital and the ability of the animal to regain its righting reflex within 1

min. $ED_{+300\%}$ values are recorded in Table I. $ED_{+300\%}$ is defined as the dose at which the average sleeping time of the animals in a test group is increased by 300% in comparison to that of a control group.

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Structure and Anticoccidial Activity of a New Series of 4-Hydroxyquinoline-3-carboxylates

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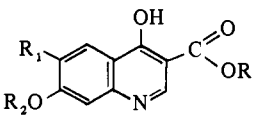
A new group of broad-spectrum coccidiostats, the 4-hydroxyquinoline-3-carboxylates (**1**), was first described by Spencer, *et al.*[1] The activity of these compounds was later confirmed in several publications.[2-4] Decoquinate[3] (**1a**),

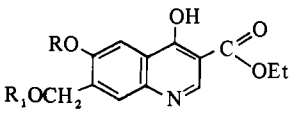


1

1a, decoquinate	**1b**, nequinate	**1c**, buquinolate
R = Et	R = Me	R = Et
$R_1 = OC_{10}H_{21}$	R_1 = *n*-Bu	R_1 = *i*-BuO
R_2 = Et	$R_2 = CH_2C_6H_5$	R_2 = *i*-Bu

nequinate[2] (**1b**), and buquinolate[1] (**1c**) are among the most effective coccidiostats known at present. These compounds all have an alkoxy substituent in position 7 and an alkyl or alkoxy substituent in position 6.

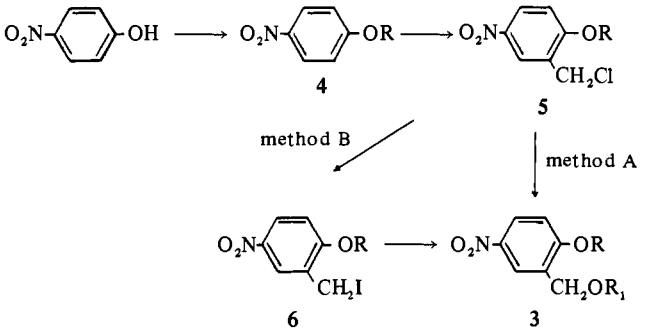
In contrast, the compounds **2** described here are ethyl 6-alkoxy-4-hydroxyquinoline-3-carboxylates with an alkoxymethyl or an aralkoxymethyl substituent in the 7 position. These compounds are also potent coccidiostats.



2

Chemistry. Nitro compounds **3** were used to initiate the synthetic pathways leading to the formation of compounds **2**. These nitro compounds themselves are synthesized as outlined in Scheme I. The reaction of *p*-nitrophenol with

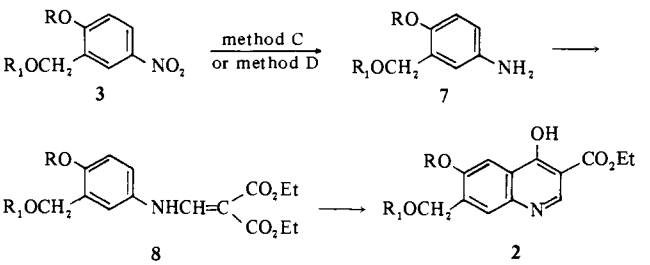
Scheme I



an appropriate alkyl halide in the presence of a base, *e.g.*, NaOH or NaOMe, yields the *p*-nitrophenoxyalkanes **4**. These alkoxynitrobenzenes may be chloromethylated using paraform, $ZnCl_2$, and gaseous HCl to produce the benzyl chlorides **5**. The desired nitro compounds **3** may be formed by the reaction of sodium alcoholates with benzyl chlorides (method A) although various side products and tars are frequently obtained. Therefore, the more usual procedure is to have the chlorides react with NaI in acetone to obtain benzyl iodides **6** (method B). High yields of the desired benzyl ethers **3** may be readily obtained by addition of appropriate alcohols to the system. Most of the benzyl halides, summarized in Table I, are novel.

The pathway starting with benzyl ethers **3**, as outlined in Scheme II, is used for the final synthesis of compounds

Scheme II



2. The nitro compounds **3** may be reduced to their corresponding anilines **7** by two different methods: either catalytic reduction with PtO_2 in ethanol (method C) or reduction with ammonium chloride and iron (method D). These anilines are condensed with diethyl methoxymethylenemalonate in boiling ethanol or 2-propanol.

Only a limited number of condensation products **8** were isolated, the majority being used in their crude form for the last stage of the synthesis. Ring closure of compounds **8** was effected by heating in diphenyl ether or diphenylmethane, both solvents being equally suitable (Table II).

Chemotherapy. For screening purposes, 18-day-old male Hisex chickens weighing between 100 and 120 g were housed in individual cages for the duration of the experiment. Feed, known not to contain coccidiostat, was available at will. On day 0, the chickens were divided into three groups: four noninfected, nontreated birds; four infected, nontreated birds; two infected, treated birds. Coccidiosis was induced by inoculation of the test animals with approximately two million sporulated oöcysts of *Eimeria Acervulina*. For 6 days, the treated birds were given the compounds **2** at will at a dose of 0.01% of their feed. On the seventh day, the medicated feed was replaced by normal feed for five subse-