pound was prepared from 3.8 g (0.02 mole) of IIc and 0.02 mole of III by essentially the same procedure as described for the preparation of IVa. Recrystallization from abs EtOH gave 3.65 g (38%) of IVc: mp 168–171°; λ_{max}^{EtOH} 226 (ε 29,000), 291 (7000), and 342 mμ (5300). *Anal.* ($C_{22}H_{26}ClN_3O_7$) C, H, N, Cl^-.

3-[2-Oxo-3-*cis*-(3-methoxy-2-piperidyl)propyl]-5,6-methylenedioxy-4-quinazolone (Ve).—A mixture of 2.40 g (0.005 mole) of IVc and 50 ml of 6 *N* HCl was boiled for 1 hr. The mixture was evaporated to dryness on a steam bath under reduced pressure. After addition of abs EtOH the residue was again evaporated to dryness. The solid product thus obtained was triturated with EtOH and filtered to give 2.0 g (95% yield) of white crystals, mp 207–210°. Further recrystallization with the addition of dry HCl yielded Ve as its dihydrochloride, mp 212–214° dec. Absorption bands of spectra (uv, ir) were as expected. *Anal.* ($C_{18}H_{23}N_3O_5 \cdot 2HCl$) C, H, N, Cl^-. When no additional HCl was introduced during recrystallization, the final product was found to be a monohydrochloride. *Anal.* ($C_{18}H_{23}N_3O_5 \cdot HCl$) C, H, N, Cl^-.

3-Hydroxy-α-picoline (XIII).—To a solution of 106.4 g (0.17 mole) of 2-dimethylaminomethyl-3-hydroxypyridine[42] in 300 ml of Me_2CO was slowly added, with stirring, 99.4 g (0.7 mole) of MeI. The reaction mixture was cooled in an iced H_2O bath to keep the temperature of the reaction mixture below 30°. The quaternary ammonium salt XII started to precipitate in 1 hr. After the mixture was allowed to stand overnight at room temperature, the solid was collected by filtration to give 198 g of *N*-(3-hydroxy-2-picolyl)trimethylammonium iodide (XII) as white crystals, mp 150–160° dec. It was used for the following hydrogenation reaction without further purification.

A solution of 58.8 g (0.2 mole) of XII in 200 ml of 5% NaOH was hydrogenated in the presence of 0.6–0.7 g of 10% Pd C. The absorption of 1 equiv of H_2 was completed within 5 hr. The catalyst was filtered and the filtrate was first made acidic with AcOH, then brought to pH 8–9 with NH_4OH. The solution was concentrated to a small volume. The resulting precipitate was collected by filtration, washed with H_2O, and dried in air. The average yield of more than 20 runs was 9.8 g (45%), mp 165–167°. Recrystallization from EtOAc gave 2-hydroxy-α-picoline as white crystals, mp 168.5–169.5°, lit. mp 163–165°,[42] 167–168°.[43] *Anal.* (C_6H_7NO) C, H, N.

Acknowledgments.—The authors express their appreciation to Dr. Edgar A. Steck for his interest in this investigation and to Mrs. Margaret L. Rounds and Mr. John R. Gravatt for their valuable assistance in performing analytical and instrumental measurements.

(42) A. Stempel and E. C. Buzzi, *J. Amer. Chem. Soc.*, **71**, 2069 (1949).

(43) A. Dornow, *Ber.*, **73B**, 78 (1940).

Structure and Anticoccidial Activity among Some 4-Hydroxyquinolinecarboxylates

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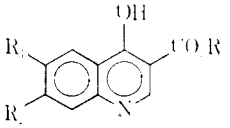
Structure requirements for anticoccidial activity have been elucidated for a series of 4-hydroxyquinoline-3-carboxylates.

Recent publications[1] have revealed that certain 6,7-disubstituted-4-hydroxy-3-quinolinecarboxylate esters are highly effective against a broad spectrum of coccidia. The most effective drugs in present use are **1**, **2**, and **3**, with **2** and **3** being the most potent.



1 (Buquinolate), R_1, R_2 = *i*-BuO; R_3 = Et

2 (Decoquinate), R_1 = $C_{10}H_{21}O$; R_2, R_3 = EtO

3 (Methylbenzoquate), R_1 = *n*-Bu; R_2 = $PhCH_2O$; R_3 = Me

Certain structure–activity relationships are apparent from published results.

(1) **R_1 = R_2 = Alkoxy.**—Maximum activity is obtained at about C_4 with rapid fall-off beyond. Branched-chain aliphatics are more effective than straight-chain.

(2) **R_1, R_2 = Alkoxy ($R_1 \neq R_2$).**—Nonidentical aliphatic ether groups in general confer higher anticoccidial potency. Activity seems to peak where R_1 is $(C_8\text{-}C_{14})$-O and R_2 is lower alkoxy.

(3) **R_1 = Alkyl; R_2 = Benzyloxy.**—High activity results for R_1 = Bu. Potency drops off where $R_1 < C_4H_9$.

(4) **Substitution in the 6 and 7 positions** seems to be essential for superior activity.

Our longtime interest in this class of compounds originated in connection with another problem. Applications of a lead developed in another series[2] gave ethyl 6,7-bis(cyclopropylmethoxy)-4-hydroxy-3-quinolinecarboxylate (cyproquinidate), an active coccidiostat.[3] The high biological activity of this substance prompted a comprehensive study to include compounds of types **4–7**.

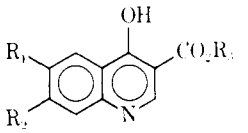
The preparation of **4** and **5** was carried out in a conventional manner as shown in Scheme I.

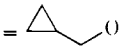
Compounds of type **6** were prepared from *m*-acyloxyacetanilide (Scheme II) and **7** resulted by application of the same synthetic sequence to the *p*-acyloxyacetanilide.

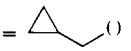
(1) C. F. Spencer, A. Engle, C.-N. Yao, R. C. Finch, E. J. Watson, E. Eberius, and C. A. Johnson, *J. Med. Chem.*, **9**, 934 (1966); J. F. Ryley, *Brit. Vet. J.*, **123**, 513 (1967); *J. Parasitol.*, **53**, 1151 (1967); J. N. Hogebom, *Brit. Vet J.*, **124**, 209 (1968).

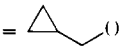
(2) R. H. Mizzoni, F. Goble, E. Konopka, J. Gelzer, J. E. Brown, J. Boxer, J. Szanto, D. C. Maplesden, and G. deStevens, *J. Med. Chem.*, in press.

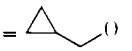
(3) R. H. Mizzoni, F. Goble, J. Szanto, D. C. Maplesden, J. E. Brown, J. Boxer, and G. deStevens, *Experientia*, **24**, 1188 (1968).



4. R_1 = 
$R_2 = C_nH_{2n+1}O$
R_3 = alkyl

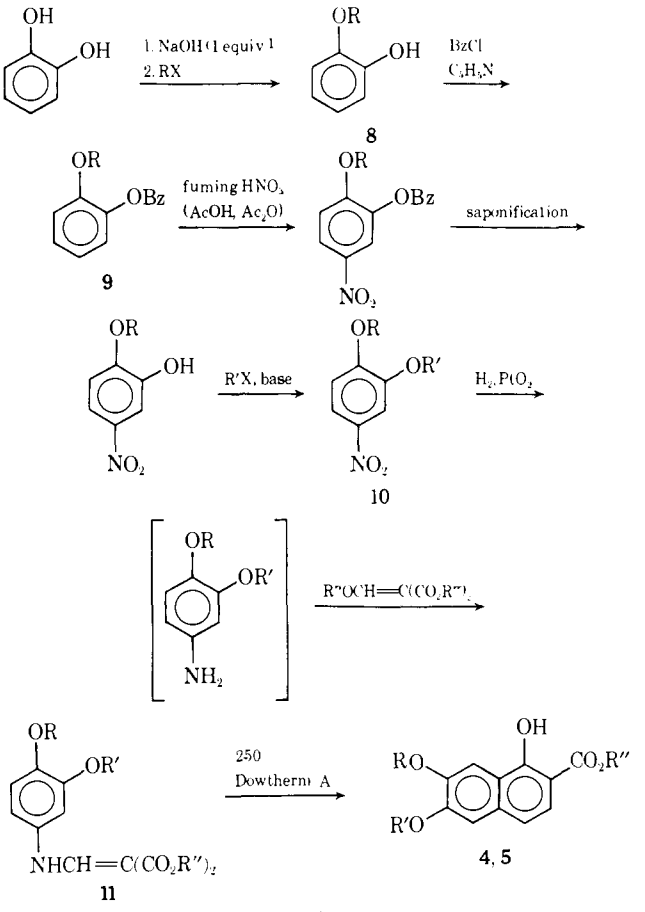
5. $R_1 = C_nH_{2n+1}O$
R_2 = 
R_3 = alkyl

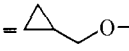
6. R_1 = alkyl, alkenyl
R_2 = 
R_3 = alkyl

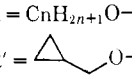
7. R_1 = 
R_2, R_3 = alkyl

In other examples the synthesis of 6,7- and 7,8-disubstituted 4-hydroxy-3-quinolinecarboxylates is shown in Scheme III.

SCHEME I

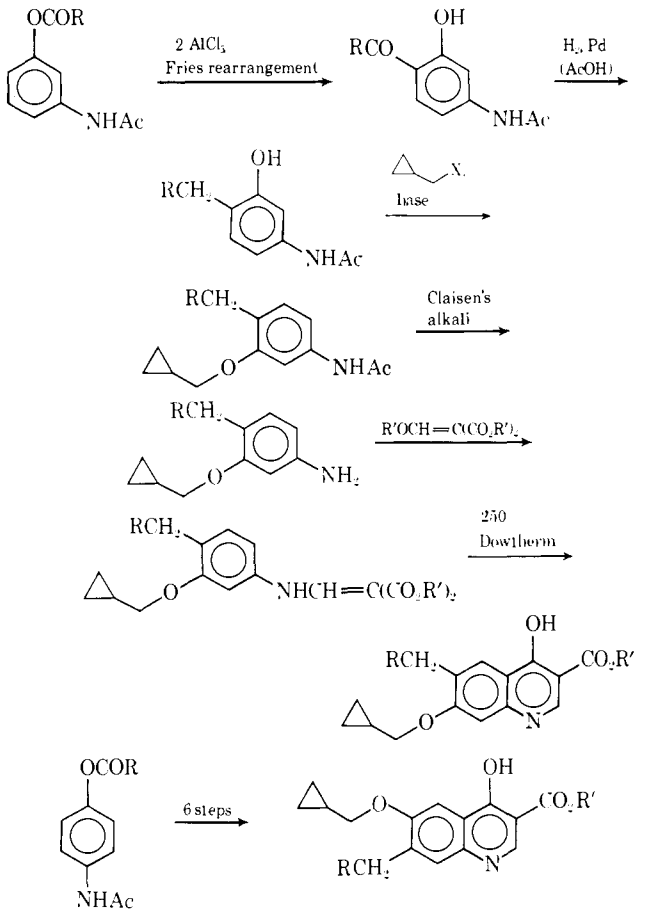


6a-11a, R = 
R' = $C_nH_{2n+1}O$—

6b-11b, R = $C_nH_{2n+1}O$—
R' = 

X = Cl or Br (See Experimental Section)

SCHEME II



Claisen rearrangement of *m*-allyloxyacetanilide was reported by Arnold and coworkers[4] to give **19**. More recently, however, Buděšínský and Ročkova[5] showed that **20** is formed as a side product. We found that the two isomers were produced, with **19** predominating; they were separated by fractional precipitation of the phenols from a mixture of the Na salts. Conventional synthetic methods then gave **24** and **29**.

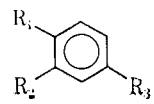
Biological Results. A.—As a primary screening method compounds were tested against one species of coccidia (*Eimeria tenella*) as follows.

One-day old Leghorn chicks, purchased from Shamrock Farms, North Brunswick, N. J. 80902, were kept in electric brooders for 7 days. They were then divided into appropriate experimental and control groups comprised of 5–10 birds each and placed into cages heated with light bulbs. The 8-day old chicks were inoculated into their crops with approximately 2×10^5 sporulated oocysts of *E. tenella* by intubation. One day prior to infection the regular starter feed was replaced by medicated diet consisting of feed with the drug incorporated by mixing in a rotating V-shaped mechanical mixer. Compounds were tested initially at 0.05% dose level in the feed. In the event of positive coccidiostat activity the dose level was reduced in subsequent experiments to determine the minimal concentration exhibiting anticoccidial efficacy. Death from coccidiosis among un-

(4) R. T. Arnold, J. McCool, and E. Scholtz, *J. Amer. Chem. Soc.*, **64**, 1023 (1942).

(5) Z. Buděšínský and E. Ročkova, *Chem. Listy*, **48**, 427 (1954); *Chem. Abstr.*, **49**, 3880c (1955).

TABLE I



No.	R_1	R_2	R_3	Procedure	Yield, %	Mp or bp °C (mm)	Formula	Analyses	Notes
1	PrCO	OH	AcNH	I	85.0	115–117	$C_{12}H_{15}NO_3$	C, H, N (nmr, ir)	
2	PrCO		$NHCH{=}C(CO_2Et)_2$	T		62–65		(Nmr)	*a*
3	PrCO		NH_2	S	45.3	85.5–88	$C_{14}H_{19}NO_2$	N (nmr, ir)	
4	*n*-Bu	OH	AcNH	J	73.0	143–145	$C_{12}H_{15}NO_2$	C, H, N (nmr)	
5	*n*-Bu		AcNH	K	47.0	77–79	$C_{16}H_{23}NO_2$	C, H, N (nmr)	
6	*n*-Bu		$NHCH{=}C(CO_2Et)_2$	T		Oil			*a*
7	*n*-Bu		$NHCH{=}C(CO_2Me)_2$	T		Oil			*a*
8	$CH_2{=}CHCH_2$		AcNH	K	45.1	65–67	$C_{15}H_{19}NO_2$	C, H, N (nmr)	
9	$CH_2{=}CHCH_2$		NH_2	S	55.5	98–100 (0.08)	$C_{13}H_{17}NO$	N (nmr)	*b*
10	$CH_2{=}CHCH_2$		$NHCH{=}C(CO_2Et)_2$	T	79.3	75	$C_{22}H_{27}NO_5$	C, H, N	
11	$CH_2{=}CHCH_2$	OH	AcNH	X	27.5	165–166	$C_{11}H_{13}NO_2$	C, H, N (nmr)	
12	*n*-Pr		AcNH	K		70–74	$C_{15}H_{21}NO_2$	N	
13	*n*-Pr		NH_2	S	58.0	98–104 (0.08)	$C_{13}H_{19}NO$	N (nmr)	
14	*n*-Pr	OH	AcNH	K	83.4	178–179	$C_{13}H_{15}NO_2$	C, H, N	
15	*n*-Pr		$NHCH{=}C(CO_2Et)_2$	T		Oil			*a,c*
16	$C_8H_{17}CO$	OH	AcNH	I		105–107	$C_{17}H_{23}NO_3$	N (nmr, ir)	
17	C_9H_{19}	OH	AcNH	J	61.0	120–123	$C_{17}H_{27}NO_2$	C, H, N (ir)	
18	C_9H_{19}		AcNH	K		Oil		(Nmr)	*a*
19	C_9H_{19}		$NHCH{=}C(CO_2Et)_2$	T		Oil		(Nmr)	*a*
20	OH	*n*-Bu	AcNH	J	90.3	83–85	$C_{12}H_{17}NO_2$	C, H, N (ir, nmr)	
21		*n*-Bu	AcNH	K		65–67		(Nmr)	*a*
22		*n*-Bu	$NHCH{=}C(CO_2Et)_2$	T		Dark oil		(Nmr)	*a*
23		*n*-Bu	$NHCH{=}C(CO_2Me)_2$	T		Dark oil		(Nmr)	*a*
24	OH	*n*-PrCO	AcNH	I	70.0	100.5–102	$C_{12}H_{15}NO_3$	C, H, N (ir, nmr)	
25			H	L	75.0	162 (13)	$C_{14}H_{18}O_2$	C, H, (nmr, ir)	
26			NO_2	M	80.2	80.5–81.5	$C_{14}H_{17}NO_4$	C, H, N (nmr, ir)	
27			$NHCH{=}C(CO_2Et)_2$	N		66–67		C, H, N	
28			$NHCH{=}C(CO_2Me)_2$	N	78.4	68–69			
29			NO_2	M	31.0	60–61	$C_{16}H_{21}NO_4$	C, H, N (nmr)	
30			$NHCH{=}C(CO_2Et)_2$	N	92.8	Oil			*a*
31	H		NO_2	W	92.8	120 (0.25)	$C_{10}H_{11}NO_3$	C, H, N (nmr)	
32	H		$NHCH{=}C(CO_2Et)_2$	N		Oil			*a*
33		Cl	NO_2	W	79.1	43–47	$C_{10}H_{10}ClNO_3$	C, H, N	
34		Cl	$NHCH{=}C(CO_2Et)_2$	N	77.2	77–78	$C_{18}H_{22}ClNO_5$	C, H, N (nmr)	
35		HO	H	A	34.2	90–94 (0.4)	$C_{10}H_{10}O_2$	C, H	*d*
36		$PhCO_2$	H	B	60.9	153–154 (0.4)	$C_{17}H_{16}O_3$	C, H (ir)	*e*
37		$PhCO_2$	NO_2	C	78.6	68	$C_{17}H_{15}NO_5$	C, H, N (ir)	
38		AcNH	NO_2	W	68.4	116–117	$C_{12}H_{14}N_2O_4$	C, H, N	

TABLE I (*Continued*)

No.	R_1	R_2	R_3	Procedure	Yield, %	Mp or bp °C (mm)	Formula	Analyses	Notes
39		AcNH	$NHCH{=}C(CO_2Et)_2$	N	75.8	135–138	$C_{20}H_{26}N_2O_6$	C, H, N (ir, nmr)	
40	AcNH		NO_2	W	50.8	113–114	$C_{12}H_{14}N_2O_4$	C, H, N (nmr)	
41	AcNH		$NHCH{=}C(CO_2Et)_2$	N	85.0	107–108	$C_{20}H_{26}N_2O_6$	C, H, N (nmr)	
42		HO	NO_2	D	47.7	104–105	$C_{10}H_{11}NO_4$	C, H, N	
43		*n*-PrO	NO_2	E	76.9	73–75	$C_{13}H_{17}NO_4$	N (ir)	
44		*n*-PrO	$NHCH{=}C(CO_2Et)_2$	N	93.2	55–56	$C_{21}H_{29}NO_6$	C, H, N (nmr)	
45			NO_2	Y	95.0	87–90	$C_{14}H_{17}NO_4$	C, H, N	
46		*i*-BuO	$NHCH{=}C(CO_2Et)_2$	N		Oil			*a*
47		*i*-AmO	NO_2	E	59.7	63–64	$C_{15}H_{21}NO_4$	N (ir)	
48		*i*-AmO	$NHCH{=}C(CO_2Et)_2$	N	85.0	30–31	$C_{23}H_{33}NO_6$	C, H, N (ir)	
49		$PhCH_2O$	NO_2	E	80.0	91–92	$C_{17}H_{17}NO_4$	C, H, N (ir)	
50		$PhCH_2O$	$NHCH{=}C(CO_2Et)_2$	N		Oil			*a*
51		$C_8H_{17}O$	NO_2	E	93.5	48–49	$C_{18}N_{27}NO_4$	C, H, N	*a*
52		$C_8H_{17}O$	$NHCH{=}C(CO_2Et)_2$	N		Oil		(Nmr)	*a*
53		$C_{10}H_{21}O$	NO_2	E	72.0	59–61	$C_{20}H_{31}NO_4$	C, H, N (nmr, ir)	
54		$C_{10}H_{21}O$	$NHCH{=}C(CO_2Et)_2$	N	95.0	41–43	$C_{28}H_{43}NO_6$	(Nmr)	
55		$C_{10}H_{21}O$	$NHCH{=}C(CO_2Me)_2$	N		Oil		(Nmr)	*a*
56		$C_{12}H_{25}O$	NO_2	E		Amorphous		(Ir)	*a*
57		$C_{12}H_{25}O$	$NHCH{=}C(CO_2Et)_2$	N		Oil		(Nmr, ir)	*a*
58	$C_{10}H_{21}O$		NO_2	E	81.2	61–62	$C_{20}H_{31}NO_4$	(Nmr)	*a*
59	$C_{10}H_{21}O$		$NHCH{=}C(CO_2Et)_2$	N		Dark oil		(Nmr)	*a*
60		$C_{14}H_{29}O$	NO_2	E	69.0	63–64	$C_{24}H_{39}NO_4$	C, H, N (ir)	
61		$C_{14}H_{29}O$	$NHCH{=}C(CO_2Et)_2$	N	Quant	56–57	$C_{32}H_{51}NO_6$	C, H, N (nmr)	
62	*n*-PrCO		AcNH	E	52.3	128–129	$C_{16}H_{21}NO_3$	N(nmr)	
63	AcO	AcO	$NHCH{=}C(CO_2Et)_2$	N	87.9	124–125	$C_{18}H_{21}NO_8$	C, H, N (nmr, ir)	
64	H	$C_8H_{17}CO_2$	AcNH	H	84.0	43–45	$C_{17}H_{25}NO_3$	C, H, N (ir)	
65	$C_8H_{17}CO$	OH	AcNH	I	55.0	105–107	$C_{17}H_{25}NO_3$	N (nmr, ir)	
66	C_9H_{19}	OH	AcNH	J	61.0	120–123	$C_{17}H_{27}NO_2$	C, H, N (ir)	
67	C_9H_{19}		AcNH	K		Oil		(Nmr)	*a*
68	C_9H_{19}		$NHCH{=}C(CO_2Et)_2$	T	Quant	Oil		(Nmr)	*a*
69	C_9H_{19}		NH_2	S		Oil		(Ir)	*a*

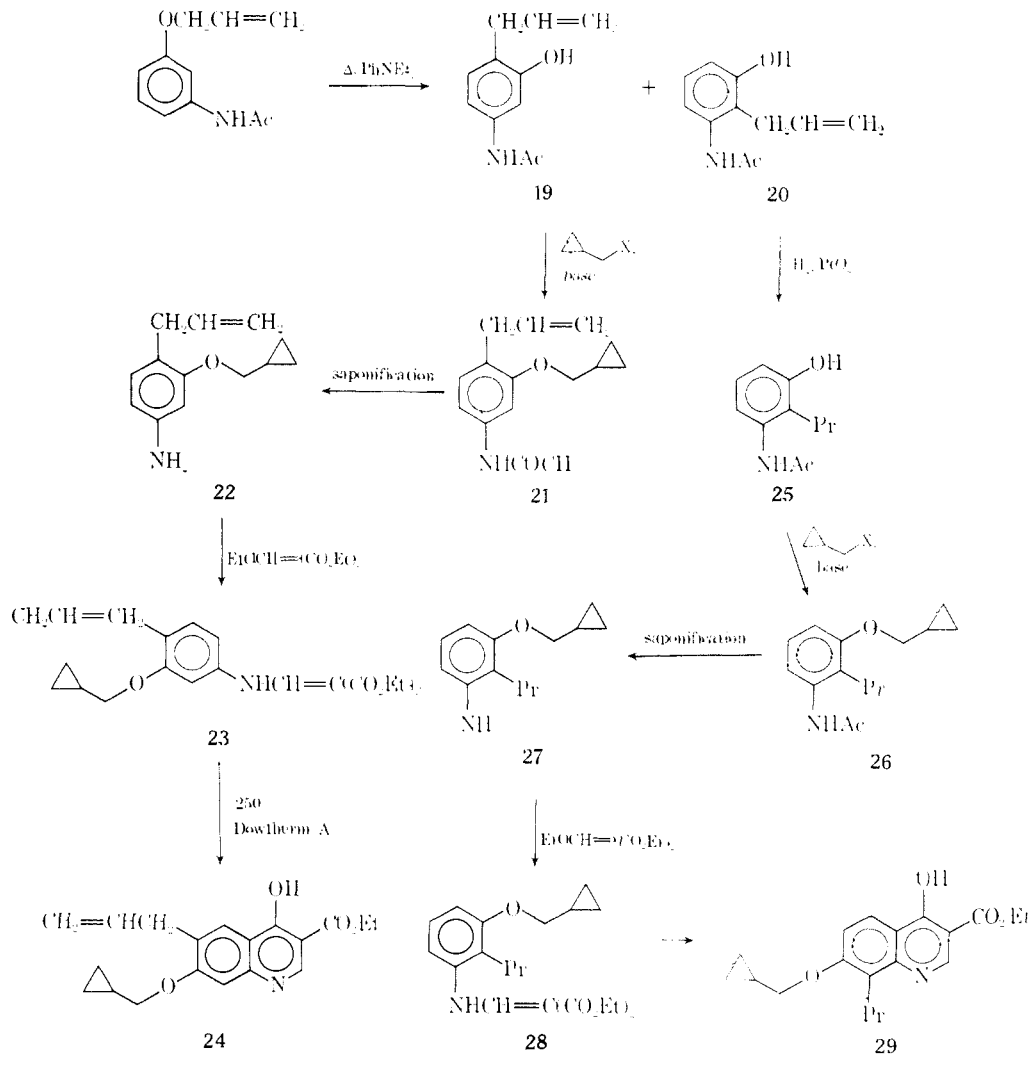
[a] Material carried through to next step without further purification. [b] Glpc analysis indicated 99% purity. [c] Tlc indicates presence of one component. [d] 98.4% purity by glpc. [e] 99.3% purity by glpc.

medicated control birds started about 4 days after infection; by day 9, 90% or more were dead.

For evaluation of coccidiostatic activity, the cumulative mortality on day 8 after infection was determined in control and treated birds. An 80% protection was considered a marked coccidiostatic effect.

B.—A more rigorous efficacy test against a mixed coccidial infection was carried out in battery cages on compounds with activity against *E. tenella*. One-day old Peterson Cross (Peterson males x Arbor Acres females) broiler chicks obtained from a commercial hatchery were raised in battery brooders for 2 weeks before the test. Ten birds, 5 males and 5 females, were randomly selected for each group. The treatments were replicated 2, 3, or 4 times. Feed was available to the chicks *ad libidum*. The medicated feed was offered starting 2 days before infection, the only feed throughout the trial period. The coccidial inoculum was prepared by mixing a calculated number of sporulated oocysts from pure cultures of *E. acervulina*, *E. brunetti*, *E. maxima*, *E. necatrix*, and *E. tenella*. The inoculum was administered into the crop to each individual chick with an automatic pipetting syringe equipped with a No. 7 venous cannula. The criteria of anticoccidial

Scheme III



activity were weight gain, feed conversion, survival, fecal dropping score, and oocyst output.

Discussion of Biological Results

The beneficial results noted for ethyl 6,7-bis(cyclopropylmethoxy)-4-hydroxyquinoline-3-carboxylate (cyproquinidate) were increased substantially by replacement of one of the ether groups by a long-chain alkoxy substituent. The greatest effect was attained with ethyl 6-cyclopropylmethoxy-7-decyloxy-4-hydroyxquinoline-3-carboxylate (**83**, Table III), although the 7-octyloxy (**81**) and 7-dodecyloxy (**84**) were almost as active. A less beneficial effect was noted with the 7-cyclopropylmethoxy-6-decyloxy isomer (**88**).

Anticoccidial activity was also demonstrated for ethyl 7-butyl-6-cyclopropylmethoxy-4-hydroxyquinoline-3-carboxylate (**95**); the 6-butyl-7-cyclopropylmethoxy compound, however, was less active than its isomer. Furthermore, unsaturation in the alkyl group (**92**) or introduction of an oxo function (**100**) lead to a decrease in activity.

Shifting the carbethoxy grouping to the 2 position (**101**, **102**) was detrimental to the anticoccidial effect. Furthermore, moving the 6-alkyl to the 8 position lead to a decrease in activity.

The requirements for optimal anticoccidial activity within the context of this study, therefore, would appear to be: (1) appropriate substitution in the 6 and 7 positions; (2) a 4-hydroxy function (unpublished results show that transference of this group to the 2 position is detrimental); and (3) a 3-carbalkoxy group.

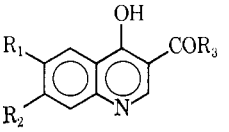
Experimental Section

Melting points and boiling points are uncorrected. Procedures are typical and are adaptable with minor changes where indicated.

Procedure A. 2-Cyclopropylmethoxyphenol.—A mixture of 55.0 g (0.5 mole) of catechol, 20.0 g (0.5 mole) of NaOH (pulverized pellets), and 250 ml of anhydrous EtOH was refluxed for 1 hr with stirring under N_2. Precipitation of the Na salt occurred during this period. Cyclopropylmethyl bromide (86.9 g, 0.55 mole) was added over 15 min, followed by stirring and refluxing for 24 hr. The reaction mixture was concentrated to about one-third the original vol and diluted with H_2O. The product was extracted with several portions of CH_2Cl_2. The washed extract was dried and stripped of solvent. The oily product was distilled *in vacuo*, bp 85–91° (0.1 mm) (43 g). Redistillation gave 28.3 g of material, bp 90–94° (0.4 mm), with a purity of 98.4% by glpc.

Procedure B. o-Cyclopropylmethoxyphenyl Benzoate. A mixture of 6.8 g (0.17 mole) of NaOH (pulverized pellets), 28.3 g of the catechol monoether, and 100 ml of anhydrous EtOH was refluxed and stirred for 0.5 hr. The fluffy solid was filtered off on cooling and dried quickly on a Buchner funnel. The solid was suspended in 300 ml of C_6H_6 and stirred under N_2 while 23.9 g (0.17 mole) of BzCl was added, dropwise at 25°. Temperature

TABLE II



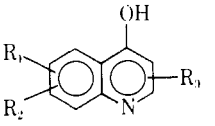
No.	R_1	R_2	R_3	Yield, %	Mp, °C	Empirical[a] formula
70			EtO	79.6	290–290.5 dec	$C_{20}H_{23}NO_5$
71			MeO	52.0	269–272 dec	$C_{19}H_{21}NO_5$
72			EtO	69.4	299–302	$C_{22}H_{27}NO_5$
73		H	EtO	63.9	265–268	$C_{16}H_{17}NO_4$
74		Cl	EtO	66.4	293–294 dec	$C_{16}H_{16}ClNO_4$
75		AcNH	MeO	49.0	183–184	$C_{17}H_{18}N_2O_5$
76		AcNH	EtO	35.2	280–285 dec	$C_{18}H_{20}N_2O_5$
77			$NHNH_2$	55.6	265–267 dec	$C_{18}H_{21}N_3O_4$
78		*n*-PrO	EtO	70.8	273–275 dec	$C_{19}H_{23}NO_5$
79		*i*-BuO	EtO		285	$C_{20}H_{25}NO_5$
80		*i*-AmO	EtO	74.6	269–270 dec	$C_{21}H_{20}NO_5$
81		$C_8H_{17}O$	EtO	34.5	256–258	$C_{24}H_{33}NO_5$
82		$C_{10}H_{21}O$	MeO	16.0	253–254	$C_{25}H_{35}NO_5$
83		$C_{10}H_{21}O$	EtO	64.5	253–254	$C_{26}H_{37}NO_5$
84		$C_{12}H_{25}O$	EtO	27.8	210–213	$C_{28}H_{41}NO_5$
85		$C_{14}H_{29}O$	EtO	60.0	237–238	$C_{30}H_{45}NO_5$
86		$PhCH_2O$	EtO	55.9	294–295 dec	$C_{23}H_{23}NO_5$
87	AcNH		EtO	22.3	325–327	$C_{18}H_{20}N_2O_5$
88	$C_{10}H_{21}O$		EtO	26.1	234–235	$C_{26}H_{37}NO_5$
89	C_4H_9		MeO	38.1	285–287 dec	$C_{19}H_{23}NO_4$
90	*n*-Bu		EtO	36.4	292–293 dec	$C_{20}H_{25}NO_4$
91	*n*-Pr		EtO	48.4	292–293	$C_{19}H_{23}NO_4$
92	$CH_2{=}CHCH_2$		EtO	55.0	293–295	$C_{19}H_{21}NO_4$
93	C_9H_{19}		EtO	11.4	255	$C_{25}H_{35}NO_4$
94		*n*-Bu	MeO	61.7	257–259 dec	$C_{19}H_{23}NO_4$
95		*n*-Bu	EtO	68.0	259–261 dec	$C_{20}H_{25}NO_4$
96	*i*-BuO		EtO	73.0	285	$C_{20}H_{25}NO_5$
97	HO	HO	EtO	80.0	287–289 dec	$C_{12}H_{11}NO_5$
98	AcO	AcO	EtO	57.5	311–313 dec	$C_{16}H_{15}NO_7$
99	H		EtO	63.9	>290	$C_{16}H_{17}NO_4$
100	*n*-PrCO		EtO	77.8	298.5–299 dec	$C_{20}H_{23}NO_5$

[a] All compds were analyzed for C, H, N.

control was effected with an ice-water bath. Stirring was continued for 4 hr at room temperature. The mixture was washed with 200 ml of 2% NaOH and 200 ml of H_2O. The dried extract was stripped of solvent and the oily residue distilled, bp 152–155° (0.4 mm) (27.8 g).

Procedure C. 2-Cyclopropylmethoxy-5-nitrophenyl Benzoate.—To a mixture of 75 ml of fuming HNO_3 and 1100 ml of AcOH was added dropwise with efficient stirring a solution of 78 g of *o*-cyclopropylmethoxyphenyl benzoate in 75 ml of Ac_2O. During the addition (15 min) the temperature rose to 55°. After 5 hr

TABLE III



No.	R_1	R_2	R_3	Yield, %	Mp, °C	Empirical[a] formula
101	6-cyclopropyl	7-cyclopropyl	2-CO_2Et	23.5	162–163	$C_{20}H_{23}NO_5$
102	6-cyclobutyl	7-cyclobutyl	2-CO_2Et	43.0	184–185	$C_{22}H_{27}NO_5$
103	6-cyclopropyl	8-CH_3	3-CO_2Et	74.6	293.5–293.8	$C_{15}H_{19}NO_4$
104	6-cyclopropyl	8-CF_3	3-CO_2Et	43.1	195–196	$C_{17}H_{16}F_3NO_4$
105	7-cyclopropyl	8-Pr	3-CO_2Et	76.6	192–193	$C_{19}H_{23}NO_4$

[a] All compds were analyzed for C, H, N.

TABLE IV

COCCIDIOSTATIC ACTIVITY

	E. tenella		Mixed infection	
No.	Concentration of drug in feed, %	Activity	Concentration of drug in feed, %	Activity
70	0.002	Marked	0.001	Marked
71	0.025	Marked		
72	0.025	Insignificant	0.01	Inactive
74	0.025	Marked	0.0125	Inactive
75	0.05	Insignificant		
76	0.05	Insignificant		
77			0.0125	Slight
78	0.01	Marked		
79	0.006	Marked	0.00075	Marked
80	0.005	Marked		
81	0.0002	Marked	0.00025	Marked
82	0.025	Marked		
83	0.00015	Marked	0.0001	Marked
84	0.001	Marked	0.0005	Marked
85	0.0025	Marked		
86	0.025	Moderate		
87	0.05	Insignificant		
88	0.00125	Marked		
89	0.025	Moderate		
90	0.025	Insignificant		
91	0.05	Moderate		
92	0.05	Slight		
93	0.005	Marked		
94	0.0005	Marked		
95	0.0005	Marked		
96	0.006	Marked	0.001	Marked
97	0.05	Insignificant		
98	0.05	Insignificant		
99	0.025	Insignificant		
100	0.025	Insignificant		
101			0.01	Insignificant
102			0.01	Insignificant
103	0.05	Insignificant	0.01	Insignificant
104	0.025	Insignificant		
105	0.025	Insignificant		

the mixture was diluted with an equal vol of ice–water and stirred overnight. Two such runs were combined and the product then was extracted with several portions of CH_2Cl_2. The extract was washed with H_2O and dried. Removal of the solvent gave a yellow oil. Trituration with pentane followed by solution in *i*-PrOH and careful dilution with pentane (with chilling and scratching) gave 144 g of a white solid, mp 68°. The structure was confirmed by analysis and nmr.

Procedure D. 2-Cyclopropylmethoxy-5-nitrophenol.—A solution of 40 g of 2-cyclopropylmethoxy-5-nitrophenyl benzoate, 160 ml of 95% EtOH, and 11.5 g of NaOH (pulverized pellets) was refluxed for 2 hr under N_2. The cooled solution was treated with 300 ml of H_2O and then acidified with 40 ml of concentrated HCl. The product was extracted with 400 ml of CH_2Cl_2. The extract was then stirred for 2 hr with 500 ml of 10% aqueous $NaHCO_3$. The layers were separated and the extract washed once with 100 ml of H_2O. The organic layer was dried ($MgSO_4$) and evaporated, leaving a yellow product (13.0 g) mp 104–105°. The product was essentially pure as indicated by analysis, nmr, and ir.

Procedure E. 2-Cyclopropylmethoxy-5-nitrophenyl Tetradecyl Ether.—A suspension of 10.0 g (0.048 mole) of 2-cyclopropylmethoxy-5-nitrophenol in 90 ml of PhMe was mixed with 1.92 g (0.048 mole) of pulverized NaOH pellets. The mixture was stirred under N_2 at reflux temperature for 1 hr. A red salt separated out during the reaction. After removal of the solvent *in vacuo* the residue was mixed with 90 ml of DMF, 0.25 g of NaI, and 15.2 g (0.048 mole) of tetradecyl bromide [bp 176–177° (15 mm); glc, 91% purity]. The reaction was allowed to proceed with stirring at 120° for 20 hr. The cooled reaction mixture was diluted with 400 ml of H_2O, and the tan precipitate was extracted with CH_2Cl_2. The product, obtained on removal of the solvent, was recrystallized from a small amount of hexane (13.5 g, 69%), mp 63–64°.

Procedure F. Diethyl [(4-Cyclopropylmethoxy-3-tetradecyloxyanilino)methylene]malonate.—A solution of 13.5 g (0.033 mole) of 2-cyclopropylmethoxy-5-nitrophenyltetradecyl ether in 100 ml of anhydrous EtOH was hydrogenated at 3 atmospheres in the presence of 0.5 g of PtO_2. The solution was refluxed with 7.1 g (0.033 mole) of diethyl ethoxymethylenemalonate for 5 hr. The catalyst was filtered off and the solvent distilled *in vacuo*. The product (18.0 g, 100%), mp 56–57°, was essentially pure by analysis and nmr.

Procedure G. Cyclization of Substituted Dialkyl Anilinomethylenemalonates.—In general the compounds were dissolved in 6–10 parts of Dowtherm A and refluxed for periods of 6 to 20 min. Beneficial effects are obtained by removing formed EtOH with a stream of N_2. In most cases the products were obtained in high purity. They were generally quite insoluble in most solvents and may frequently be recrystallized from boiling DMF.

Example.—A solution of 18.0 g of diethyl [(4-cyclopropylmethoxy-3-(tetradecyloxyanilino)methylene]malonate in 110 ml of Dowtherm A was refluxed at *ca.* 255° for 8 min. The reaction mixture was cooled to room temperature and diluted with a large vol of pentane. The filtered solid was washed thoroughly with pentane and dried at 80–100 *in vacuo*. The product (10.0 g, 60%), mp 237–238° was essentially pure by analysis and nmr.

Procedure H. *p*-Acetamidophenyl Butyrate.—A solution of 60 g of *p*-hydroxyacetanilide and 44 g of PrCOCl in 200 ml of pyridine was allowed to stand for 3 hr at room temperature. A crystalline product separated out during the reaction period. The mixture was diluted (H_2O), and the precipitate was filtered and washed thoroughly with H_2O until the odor of pyridine had disappeared. Recrystallization from *i*-PrOH gave 65.3 g (74.3%) of product, mp 144.5–146°.

Procedure I. 3-Butyryl-4-hydroxyacetanilide.—A mixture of 53.3 g of *p*-acetamidophenyl butyrate and 79 g of anhydrous $AlCl_3$ was heated carefully to 175° (bath temperature) with occasional hand stirring. A slow evolution of HCl took place.

After 0.5 hr the mass was ground in a mortar and reheated as before for 2.5 hr. The cooled solid was added to a mixture of ice and 2 *N* H_2SO_4 and stirred until crystalline. The product was filtered off, washed freely with H_2O, and then dissolved in 5% NaOH. The filtered solution was acidified with AcOH. The washed and dried product was recrystallized from C_6H_6 to give 42.3 g of material, mp 100.5–102°. A second crop (2.6 g) had mp 99.5–99.8°.

Procedure J. 3-Butyl-4-hydroxyacetanilide.—A solution of 45.8 g of 3-butyryl-4-hydroxyacetanilide in 500 ml of AcOH was hydrogenated at 35.15 kg/cm² in the presence of 15 g of 10% Pd–C. The catalyst was filtered off and the solvent removed *in vacuo*. The colorless oil was triturated repeatedly with hexane and crystallization was induced by chilling the hexane suspension in a Dry Ice bath with scratching (37.5 g), mp 83–85°. *Anal.* ($C_{12}H_{17}NO_2$) C, H, N.

Procedure K. 3-Butyl-4-cyclopropylmethoxyacetanilide.—A solution of 37.5 g of 3-butyl-4-hydroxyacetanilide in 100 ml of DMF was added over 0.5 hr to a suspension of 8.2 g of NaH (56.9% oil dispersion) in 100 ml of DMF (under N_2) with stirring. Temperature was controlled by an ice bath. After 1 hr at room temperature 43.0 g of cyclopropylmethyl bromide was added over 20 min. The reaction was exothermic to 50°; stirring was continued for 5 hr at 75°. The cooled mixture was filtered and the solvent removed *in vacuo* on a rotary evaporator. Petroleum naphtha was added and crystallization induced by chilling in a Dry Ice bath and scratching (54.0 g), mp 65–67°.

Procedure L. 1,2-Bis(cyclopropylmethoxy)benzene. a.—To a solution of 11.0 g of catechol in 380 ml of DMF there was added, with stirring under N_2, 11.3 g of commercial NaOMe. The solution was stirred for 1 hr at 40–45°; 32.8 g of cyclopropylmethyl bromide (85% by glpc) was then added over 0.5 hr. The mixture was stirred for 16 hr at room temperature and then for 3 hr at 75°. The pH was adjusted to *ca.* 5 after dilution with H_2O and the product taken up with several portions of CH_2Cl_2. The combined extract was washed with 10% NaOH and once with H_2O. The solvent was removed and the product distilled, bp 162° (13 mm) (14.9 g, 68.3%).

b.—To a suspension of 8.6 g of NaH (56% oil dispersion) in 200 ml of DMF a solution of 11.0 g of catechol in 180 ml of DMF was added at 10°. The mixture was stirred for 2.5 hr at room temperature; 32.8 g of cyclopropylmethyl bromide (84% by glpc) was then added over 45 min. Stirring was continued for 18 hr at room temperature. The solution was cooled with the cautious addition of 100 ml of H_2O. After further dilution with 1 l. of H_2O the product was extracted with 4 portions of CH_2Cl_2. The extract was washed with 10% NaOH and H_2O. The dried extract was stripped of solvent and the residue distilled, bp 160–164° (13 mm) (16.5 g, 75.6%).

Procedure M. 1,2-Bis(cyclopropylmethoxy)-4-nitrobenzene. a.—A solution of 12.0 g of NaOH in 30 ml of H_2O was added to a solution of 20.5 g of 4-nitrocatechol in 40 ml of 95% EtOH with stirring under N_2. After 15 min the solution was diluted with a large vol of Me_2CO. The salt was filtered under N_2, washed with Me_2CO, and dried in a vacuum desiccator. A 39.2-g quantity of the salt thus obtained was dissolved in 900 ml of DMSO and warmed to 50–55° under N_2. A 46.4-g quantity of cyclopropylmethyl bromide (85% by glpc) was added dropwise with stirring. After 6 hr at 60° the mixture was poured into ice–water. The solid was filtered off and recrystallized from *i*-PrOH (16.5 g), mp 78.5–79.5.

b.—Vigorously stirred, 1:1 aqueous HNO_3 (60 ml) was maintained at room temperature while 11.6 g of 1,2-bis(cyclopropylmethoxy)benzene was added portionwise over 0.25 hr. After 2.5 hr the heterogeneous mixture was poured over cracked ice. The product was extracted with 3 portions of CH_2Cl_2, and the extract was washed with H_2O until the washings were neutral. The dried extract was evaporated to dryness and the residue recrystallized from *i*-PrOH (9.0 g, 64.4%) mp 80–82°. The substance was identical with that derived under a by ir and nmr analyses.

Procedure N. Diethyl 3,4-Bis(cyclopropylmethoxy)anilinomethylenemalonate.—A solution of 13.2 g of 1,2-bis(cyclopropylenemethoxy)-4-nitrobenzene in 120 ml of anhydrous EtOH was hydrogenated at 2 atm with 1.0 g of PtO_2. Theoretical uptake occurred within a short time. The mixture was combined with 11.5 g of diethyl ethoxymethylenemalonate and refluxed under N_2 for 3 hr. The catalyst was removed by filtration; the residue remaining on distillation of the solvent was dissolved in a small amount of pentane and chilled. Scratching effected crystallization of the product (15.7 g), mp 66.5–67.5°. A second crop was obtained (2.4 g), mp 66–67°. Both crops were analytically pure.

Procedure P. Cyclopropylmethyl 4-Nitro-3-trifluoromethylphenyl Ether.—A solution of 20.0 g of 3-trifluoromethyl-4-nitrophenol in 100 ml of DMF was added slowly with stirring at 5–10° to a suspension of 4.3 g of NaH (56% oil dispersion) in 100 ml of DMF under N_2. The mixture was stirred for 2 hr at ice bath temperature and 5 hr at room temperature, and was followed by the addition of 15.3 g of cyclopropylmethyl bromide (91% by glpc) over 10 min. Stirring was continued for 18 hr at room temperature and then for 6 hr at 70–80°. The solvent was removed as far as possible *in vacuo*. Addition of H_2O gave a crystalline material. The product was extracted twice with CH_2Cl_2, and the extract was washed once with 5% Na_2CO_3 and once with H_2O. The dried extract was stripped of solvent to give a mass of slightly oily crystals. Sublimation *in vacuo* yielded 15.7 g of product, mp 46–48°. The structure was verified by nmr.

Procedure Q. Diethyl 4-Cyclopropylmethoxy-2-trifluoromethylanilinomethylenemalonate.—The product of procedure P was dissolved in 100 ml of anhydrous EtOH and hydrogenated at 3 atm in the presence of 0.8 g of PtO_2. Theoretical uptake occurred within 10 min. The resultant mixture was refluxed with 13.0 g of diethyl ethoxymethylenemalonate for 3 hr. The catalyst was filtered off and the filtrate concentrated as far as possible *in vacuo*. The material which crystallized on cooling was broken up and triturated with cold pentane. The product obtained on drying (22.0 g), mp 55–58° was essentially pure by analysis and nmr.

Procedure R. Ethyl 6-Cyclopropylmethoxy-8-trifluoromethyl-4-hydroxyquinoline-3-carboxylate.—Cyclization of the above material was accomplished by refluxing in 220 ml of Dowtherm A for 20 min. The cooled mixture was diluted with pentane. The substance thus obtained was recrystallized from *i*-PrOH (Norit) to give 8.4 g, mp 195–196°.

Procedure S. 4′-Amino-2′-cyclopropylmethoxybutyrophenone.—A solution of 7.2 g of 4-acetamido-2-cyclopropylmethoxybutyrophenone and 75 ml of Claisen's alkali was refluxed with stirring for 1.5 hr. It was diluted with 125 ml of H_2O and extracted with 3 portions of CH_2Cl_2. The extract was washed once with H_2O and dried ($MgSO_4$). An off-white solid was obtained (5.0 g) which was purified by sublimation (4.8 g), mp 85.5–88° (Table I). In other cases the crude amino compound was used without further purification.

Procedure T. 4-(Diethylmalonylmethyleneamino)-2-cyclopropylmethoxybutyrophenone.—The product of procedure S was combined with 4.45 g of diethyl ethoxymethylenemalonate and 35 ml of anhydrous EtOH and refluxed for 3 hr. The solvent was removed at the aspirator to give a light yellow, viscous oil which crystallized on cooling and scratching, mp 62.5–65° (8.0 g).

Procedure U. Ethyl 6-Butyryl-7-cyclopropylmethoxy-4-hydroxyquinoline-3-carboxylate.—The foregoing material (8.0 g) was cyclized by refluxing in 80 ml of Dowtherm A for 6 min. The product, which separated on cooling and dilution with hexane, was filtered, washed successively with DMF and ether, and then dried, mp 298.5–299° dec.

Procedure V. Ethyl 6,7-Bis(cyclopropylmethoxy)-4-hydroxyquinoline-2-carboxylate.—A solution of 19.4 g of 1,2-bis(cyclopropylmethoxy)-4-nitroenzene in 200 ml of anhydrous EtOH was hydrogenated at 3 atm in the presence of 0.8 g of PtO_2. The resultant mixture was refluxed for 3 hr with 15.5 g of diethyl oxalacetate. The solvent was removed leaving 33.6 g of oily residue. This substance was combined with 340 ml of Dowtherm A and refluxed for 10 min. A precipitate formed on pouring the cooled solution into a large vol of hexane. The gum which remained was freed from Dowtherm A by repeated solution in C_6H_6 and precipitation with hexane. The crystalline material which formed was recrystallized once from Me_2CO and twice from *i*-PrOH, (7.0 g) mp 162–163°.

Procedure W. Typical Procedure for Alkylation of Substituted Nitrophenols.—A solution of 26.1 g (0.15 mole) of 2-chloro-4-nitrophenol in 50 ml of DMF was added to a suspension of 6.5 g (0.15 mole) of NaH (55.7% oil dispersion) in 75 ml of DMF with stirring under dry N_2. The reaction was mildly exothermiic. Stirring was continued for 4 hr at room temperature. Following the addition of 32.0 g (0.2 mole) of cyclopropylmethyl bromide (85% by glpc) the mixture was stirred for 5 hr at 75°. The alkylation was initially exothermic. The suspension was filtered and the solvent removed *in vacuo* on a rotary evaporator. H_2O was added and the product extracted with CH_2Cl_2. The dried, H_2O-

washed extract was concentrated and chilled in an ice bath until crystallization occurred. The low melting solid was dissolved in 50 ml of *i*-PrOH and chilled in a Dry Ice bath with the addition of a small amount of hexane to give 27.0 g of 2-chloro-1-cyclopropylmethoxy-4-nitrobenzene, mp 43–47°.

Procedure X. Claisen Rearrangement of *m*-Allyloxy Acetamide.—The *m*-allyloxy acetamide was rearranged in $PhNMe_2$ according to the procedure described by Arnold, *et al.*[3] There was obtained 34.7 g of mixed isomers, mp 135–140°, from 38.6 g of starting ether. Separation was accomplished as follows.

The phenolic mixture was dissolved in 243 ml of 1 *N* NaOH and fractionally precipitated (7 fractions) by addition of 0.5 *N* H_2SO_4 in increments to complete neutralization. The first 5 fractions of mp 157–163° were combined and recrystallized from H_2O to give 10.5 g of 3-hydroxy-4-allylacetanilide, mp 165–166°. Structural verification was made by nmr determination (DMSO).

The last 2 fractions of mp 135–149° were found to be a mixture of the above material with 2-allyl-3-hydroxyacetanilide. Purification was accomplished by 3 fractional reprecipitations and final recrystallization from aqueous MeOH, mp 146–147°.

Procedure Y. 2-Cyclopropylmethoxy-5-nitrophenyl 2-Methallyl Ether.—A solution of 68.0 g of 2-cyclopropylmethoxy-5-nitrophenyl benzoate in 500 ml of 95% EtOH was mixed with 23 g of 50% NaOH and refluxed for 2 hr. The solution was diluted with 500 ml of H_2O and distilled *in vacuo* to remove EtOH. The residue was diluted with a further 500 ml of H_2O and chilled in an ice bath. Acidification with 60 ml of concentrated HCl produced a yellow crystalline product, which was extracted with 500 ml of CH_2Cl_2. The extract was stirred overnight with 500 ml of 10% $NaHCO_3$. The organic layer was washed with 200 ml of H_2O and then evaporated to dryness under reduced pressure (51.0 g). The residue was dissolved in 100 ml of DMF. To this was added 200 ml of C_6H_6, 0.5 g of NaI, and 8.7 g of NaOH. The solution was refluxed and H_2O was removed as formed. The solution was combined with 20 g of methallyl chloride and refluxed for 3 hr. After dilution with 200 ml of H_2O, C_6H_6 was removed *in vacuo*. The crystalline solid was filtered and washed with H_2O. Recrystallization from *i*-PrOH gave 53.0 g of cyclopropylmethyl-2-methallyl-4-nitrocatechol, mp 87–90°.

6,7-Bis(cyclopropylmethoxy)-4-hydroxy-3-quinolinecarboxhydrazide.—A mixture of 3.0 g of ethyl 6,7-bis(cyclopropylmethoxy)-4-hydroxy-3-quinolinecarboxylate, 3.5 g of $N_2H_4 \cdot H_2O$ (99%), and 50 ml of anhydrous EtOH was heated for 12 hr at 150° in a sealed tube. The yellow product (1.0 g) was filtered, mp 265–267° dec, and found to be essentially pure.

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Anticoccidial Activity in 1-[2-(Cycloalkyl)- and 2-(Cycloalkylmethyl-4-amino-5-pyrimidyl)methyl]pyridinium Salts

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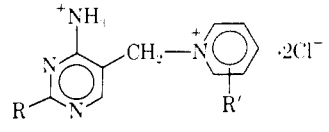
The enhanced anticoccidial activity of 1-[(4-amino-2-cyclopropylmethyl-5-pyrimidyl)methyl]picolinium and lutidinium salts is shown. Comparisons are made with other 2-cycloalkyl- and 2-cycloalkylmethyl derivatives. The structure of the 2 substituent in the types investigated was found to be critical.

In an excellent discussion of thiamine antagonists Rogers[1] outlined the parameters required of this class of antimetabolites as anticoccidial agents. The data show that certain variations are possible in the 2 or 5 positions for retention of activity. Alteration of the 4-amino group, however, leads to a loss of biological activity. Optimum anticoccidial activity was obtained in **1**.



R = Et, Pr, C_2F_5
R′ = 2-Me, 2,4-$(Me)_2$, 4-Me, 2-Me-5-Et

1

The importance of the 2 substituent in determining the degree of anticoccidial activity is demonstrated in the current literature. Thus, the Et derivative is less active than the *n*-Pr derivative, which in turn is more effective than the *n*-Bu or *i*-Bu derivatives. 2-Cycloalkyl moieties, however, have not been investigated, although on the basis of bond length alone cyclopropylmethyl approximates rather closely the length of *n*-Pr (Chart I). Consequently, substances bearing this substituent were prepared as shown in Scheme I.

The 2 substituent was further varied to include cyclopropyl, cyclobutylmethyl, and cyclopentyl as a further test of the range of activity possible with these types of substituents.

The synthetic sequence employed conventional reactions, and generally proceeded as expected. In one departure from the procedure outlined in Scheme I, 4-amino-2-cyclobutylmethyl-5-cyanopyrimidine was hydrogenolyzed directly to the 5-carbinol (Scheme II).

Biological Test Methods. A.—One-day old Leghorn chicks (Shamrock Farms, North Brunswick, N. J. 08902) were kept in electric brooders for 7 days. They were then divided into appropriate experimental and control groups comprising 5–10 birds and placed into cages heated with light bulbs. The 8-day old chicks were inoculated into their crop with approximately 2×10^5 sporulated oocysts of *Eimeria tenella* by incubation. One day prior to infection, the regular starter feed was replaced by medicated diet, consisting of feed with the drug incorporated by mixing in a rotating V-shaped mechanical mixer. Compounds were tested initially at 0.05% dose level in the feed. In case of coccidiostatic activity, the dose level was reduced in subsequent experiments to determine the minimal concentration exhibiting anticoccidial efficacy. Death from coccidiosis among unmedicated control birds started approximately 4 days after infection and by the 8th day, 90% or more were dead.

(1) E. F. Rogers, *Ann. N. Y. Acad. Sci.*, **98**, 412 (1962).