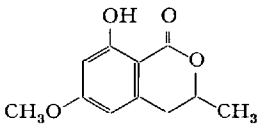
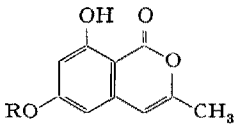
for 11 days at 25 °C. The whole broth (ca. 7 l medium) was extracted with ether and after evaporation of the ether the residue was purified by preparative thin-layer chromatography to give the isocoumarin (II) (18 mg) m.p. 129°, identical in all respects with synthetic material[12] as the major phenolic metabolite. We were unable to isolate the dihydroisocoumarin (I) but several other closely related compounds were present. One of these has been identified (by thin-layer chromatography) as the dihydroxyisocoumarin (III)[13]; others are being investigated.

The production of compounds such as (II) and (III) so closely related to (I) in a synthetic medium must throw doubt on the real origin of 6-methoxymellein in carrot infected with *C. fimbriata*, and the status of (I) as a 'phytoalexin'. These results clearly support the reservations implied by AUE et al.[9] and MCGAHREN and MITSCHER[10] and suggest that some other phytoalexins might warrant further investigation[14].



(I)



(II; R = CH_3)
(III; R = H)

Résumé. Le dihydroisocoumarin (I) était considéré comme un «phytoalexin» produit par des carottes infectées de *Ceratocystis fimbriata*. Mais l'isocoumarin (II), de structure apparentée ayant été dégagé d'une culture de ce champignon sur bouillon synthétique, on peut douter que (I) tire son origine des carottes.

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Department of Chemistry, University College of Swansea, Swansea (England), 4 July 1968.

[12] E. HARDEGGER, E. WIDMER, K. STEINER and A. PFIFFNER, Helv. chim. Acta *47*, 2022 (1964).

[13] R. F. CURTIS, P. C. HARRIES and C. H. HASSALL, J. chem. Soc. 5382 (1964).

[14] Acknowledgment. I am grateful to Prof. C. H. HASSALL for laboratory facilities, to Mr. M. J. HALL for advice and Misses J. MOLLETT and S. DARK for assistance.

Ethyl 6,7-*bis*(Cyclopropylmethoxy)-4-hydroxy-3-quinolinecarboxylate, a Potent Anticoccidial Agent

Alkyl 6,7-dialkoxy-4-hydroxy-3-quinolinecarboxylates have been shown to exhibit a good order of anticoccidial activity in the chicken[1].

Our interest in substituted 4-hydroxyquinoline-3-carboxylates, extending back to 1962, prompted us to enlarge upon some earlier work. This endeavor yielded ethyl 6,7-*bis*(cyclopropylmethoxy)-4-hydroxyquinoline-3-carboxylate (Su-18,137), a substance showing outstanding activity against a number of species of coccidia.

The synthesis of Su-18,137 is outlined in the Figure.

Catechol was alkylated with chloro- or bromo-methylcyclopropane in dimethylformamide solution containing 2 equivalents of sodium hydride (oil dispersion) to give the corresponding diether (I), $b.p._{13}$ 162°C. Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.02; H, 8.31. Found: C, 76.78; H, 8.40.

Treatment of (I) with aqueous nitric acid gave the 4-nitro derivative (II), m.p. 80.5–81.5°. Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.55; H, 6.42; N, 5.07. This substance was identical with that prepared from (III).

Catalytic hydrogenation of II in ethanolic solution in the presence of platinum oxide gave IV, which was converted to V without isolation by refluxing with 1 mole of diethyl ethoxymethylene malonate, m.p. 66–67°. Anal. Calcd. for $C_{22}H_{29}NO_6$: C, 65.49; H, 7.24; N, 3.47. Found: C, 65.90; H, 7.34; N, 3.69. Cyclization of V to VI occurred on refluxing in Dowtherm A® for 10–15 min. Anal. Calcd. for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 66.51, 66.50; H, 6.38, 6.34; N, 3.75. All structures were confirmed by means of NMR- and IR-analyses.

Biological results. Su-18,137 was mixed into chick starter feed and administered therein to 7-day-old white Leghorn chicks which were inoculated with coccidia 24 h later by intubation of sporulated oocysts into the crop. The medicated chicks were found to exhibit survival rates in this infection which caused high mortality in untreated birds. The results of 4 tests involving 3 different strains of *Eimeria tenella* are shown in Table I. Complete protection was obtained at dose levels as low as 0.0008%.

Su-18,137 was then submitted to a more rigorous test of activity. Infections with 5 species of mixed coccidia

Table I. Activity of SU-18,137 against *Eimeria tenella* in 7-day-old chicks infected with approximately 150,000 oocysts 24 h after initiation of medication in the feed (continued for 8 days)

Test No.	*E. tenella* strain	Dose level (% in feed)	No. chicks started	No. chicks surviving on day 10	% survival
1	'N'	0.0085	11	11	100
		0.00425	10	9	90
		0 (controls)	18	3	23
2	'N'	0.0032	10	10	100
		0 (controls)	20	0	0
3	'P'	0.0008	10	10	100
		0 (controls)	9	4	44
4	'S'	0.0008	8	8	100
		0 (controls)	10	3	30

[1] C. F. SPENCER, A. ENGLE, C.-N. YU, R. C. FINCH, E. J. WATSON, F. EBETINO and C. A. JOHNSON, J. med. Chem. *9*, 934 (1966). – J. F. RYLEY, Br. Vet. J. *123*, 513 (1967); J. Parasit. *53*, 1151 (1967).

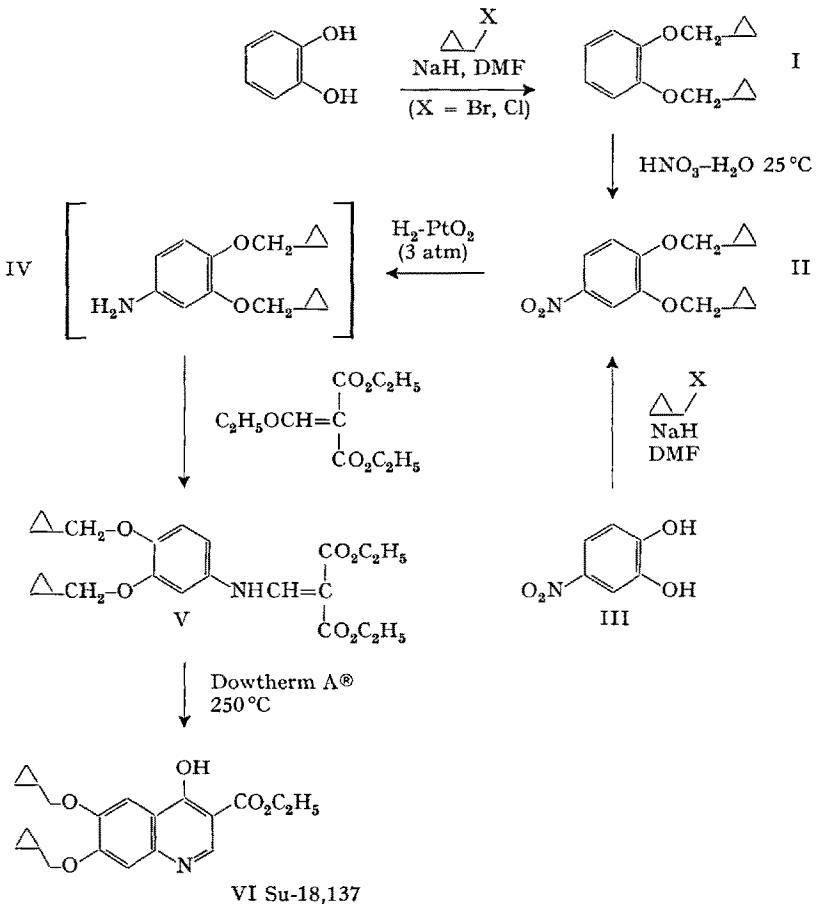

Table II. Efficacy of Su-18,137 against mixed laboratory coccidia[a] in chickens[b]

Treatment	Level in feed (%)	No. of chicks	Weight gain average g/bird day 0 to + 7	Oocyst output/ bird ($\times 10^6$)	Average mortality
Uninfected, unmedicated	–	80	143.4	0	0
Infected, unmedicated	–	80	45.2	56	43
Su-18,137	0.006	80	141.4	0	0
Su-18,137	0.0045	80	138.1	0	0
Su-18,137	0.003	80	140.0	0	0

[a] Mixture of *E. acevulina*, *E. brunetti*, *E. maxima*, *E. necatrix* and *E. tenella*. [b] 2-week-old broiler type chickens.

Table III. Comparative efficacy of Su-18,137 and Buquinolate against 6 field strains of mixed coccidia[a] in chickens[b]

Treatment	Level in feed (%)	No. of birds	Weight gain average g/bird day 0 to + 7	Oocyst output/ bird ($\times 10^6$)	Average mortality (%)
Uninfected, unmedicated	–	230	163.2	0	0
Infected, unmedicated	–	230	59.1	335.3	22.8
Su-18,137	0.0075	70	161.6	2.1	0
	0.006	200	157.7	1.6	0
	0.004	190	148.2	40.8	0
Buquinolate	0.00825	110	127.9	87.1	0

[a] Mixture of strains of: *E. acevulina*, *E. brunetti*, *E. maxima* and *E. tenella*. [b] 2-week-old broiler chickens.

(laboratory strains) were well controlled by this substance at the 0.003% feed concentration. Higher concentrations were completely effective in inhibiting oocyst production, mortality and weight loss (Table II).

Su-18,137 at the 0.004 and 0.006% levels gave good control of mixed field strains of coccidia (Table III). Each field isolate was a mixture of 6 species. The compound was found to be safe and well tolerated. Extended field trials have shown that Su-18,137 is an effective coccidiostat.

Zusammenfassung. Synthese und Wirkung gegen Coccidia des 6,7-*bis*(Cyclopropylmethoxy)-4-hydroxy-chinolin-3-carbonsäureäthylesters werden beschrieben.

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