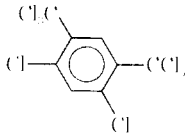
tested (**4**, **5**, **7**, **11**, **14–16**, **22**, **25**, **26**, **29**) suppressed oocysts or sporozoites of *P. gallinaceum* when fed to infected mosquitoes at a concentration of 0.1% in sucrose.[17] α,α,α,α′,α′,α′,4,6-Octachloro-*m*-xylene (II) (**8**) was examined for therapeutic action against patent *P. cynomolgi* infections in two Rhesus monkeys.[15] The



II

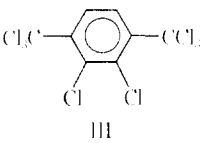
drug was given orally twice daily for 10 days. A dose of 200 mg/kg per day suppressed the parasitemia rapidly and cured the infection, while a dose of 50 mg/kg per day partially suppressed the infection but failed to cure.

α,α,α,α′,α′,α′,4,6-Octachloro-*m*-xylene (II) (**8**) was subsequently tested against representative drug-resistant lines of *P. berghei* in the mouse to determine whether or not the hexachloroxylene derivatives might represent a unique chemical type with respect to apparent mode of action. In two parallel studies **8** was administered by gavage at doses of 12, 50, and 200 mg/kg daily to mice infected with the sensitive parent line P and the following drug-resistant lines: line T, completely (>300-fold) resistant to cycloguanil; line S, completely (>600-fold) resistant to 4,4′-sulfonyldianiline (DDS); and line C, 77-fold resistant to chloroquine.[15] Groups of 10 mice were employed throughout, and treatment extended over a 4-day period starting the day before infection. The SD_{85} (daily dose required for 85% suppression of the parasitemia) for each line was as follows: line P, 114 mg/kg; line T, 57 mg/kg; line S, 132 mg/kg; line C, 150 mg/kg. Thus the chloroquine- and DDS-resistant lines were nearly as sensitive to **8** as the parent line, and there was an indication that the cycloguanil-resistant line was hypersensitive to the drug. These results suggest that the principal mode of action of **8** and the other hexachloroxylenes may be different from that of chloroquine, cycloguanil, and DDS, and encourage further chemical work aimed toward the development of more potent analogs.

Antischistosomal Studies.—Eighteen compounds (**3**, **5**, **7–11**, **13**, **15**, **17–20**, **22–24**, **26**, **27**, Table I) were tested in mice against a Puerto Rican strain of *Schistosoma mansoni*[37] by Dr. Paul E. Thompson and coworkers of these laboratories. Drugs were administered in a powdered diet for 14 days or by gavage in 10 ml/kg of aqueous 1% hydroxyethyl- or CM-cellose for 10 days. α,α,α,α′,α′,α′,4,6-Octachloro-*m*-xylene (**8**), α,α,α,α′,α′,α′,2,3-octachloro-*p*-xylene (**9**), and α,α,α,α′,α′,α′,2-heptachloro-*p*-xylene (**13**) possessed significant schistosomicidal activity and effected a 65–74% reduction of live schistosomes in infected mice at daily doses ranging from 200 to 327 mg/kg. However, none was appreciably more active than **18** which produced a 64% reduction of live schistosomes when given in the diet at 223 mg/kg per day for 7 days. All other compounds lacked significant antischistosome effects at drug–diet dose levels ranging from 105 to 346 mg/kg per day for periods of 7 or 14 days.

(37) For a description of test methods, see P. E. Thompson, J. F. Meisenhelder, and H. Najarian, *Amer. J. Trop. Med. Hyg.*, **11**, 31 (1962).

α,α,α,α′,α′,α′,2,3-Octachloro-*p*-xylene (III) (**9**) was



III

also tested against the Puerto Rican strain of *S. mansoni* in Rhesus monkeys.[37] The drug was given orally by gavage twice daily 5 days a week for 1 or 2 weeks to three monkeys. A regimen of 400 mg/kg per day for 5 days produced only a slight, temporary suppression of egg production. Regimens comprising 200 mg/kg per day for 5 days followed by 400 mg/kg per day for 5 days or 400 mg/kg per day for 10 days effected a partial permanent suppression of egg production but were not curative.

Experimental Section[38,39]

α,α,α-Trichloro-*m*-tolunitrile (15).—Cl_2 was bubbled into 98.6 g (0.84 mol) of *m*-tolunitrile at bath temp of 180° for 15.5 hr. The apparatus was irradiated with a 75-W floodlight. Distillation of the resulting product yielded 145.4 g (79%) of **15**, bp 74–76° (0.10 mm), mp 37–39°. *Anal.* ($C_8H_4Cl_3N$) C, H, N.

3,5-Bis(trichloromethyl)benzonitrile (25).—Cl_2 was bubbled into 41.0 g (0.313 mol) of 3,5-dimethylbenzonitrile[40] at 180° (oil bath temperature) for 21.5 hr. The reaction flask was irradiated with a 75-W floodlight during the chlorination. Four recrystallizations from aqueous EtOH gave 43.1 g (43%) of the desired product, mp 90–92°. *Anal.* ($C_9H_3Cl_6N$) C, H, N.

4,4′-Bis(trichloromethyl)benzophenone (29).—Cl_2 was bubbled into a melt of 20.0 g (0.095 mol) of 4,4′-dimethylbenzophenone for 15.25 hr as above. The bath temperature was steadily increased from 160 to 220° during the course of the reaction to maintain the reaction mixture as a melt. Recrystallization from cyclohexane yielded 20.4 g of product mp 202–204° and a second crop of 7.8 g, mp 197–202°, which combined represent a 71% yield. A 4.5-g sample recrystallized for analysis from 500 ml of EtOH yielded 3.4 g of material, mp 203–204°. *Anal.* ($C_{15}H_8Cl_6O$) C, H.

Acknowledgments.—The authors express their appreciation to Dr. Leo Rane of the University of Miami, and to Dr. Paul E. Thompson of Parke, Davis and Company for the antimalarial and antischistosome testing. We also thank Mr. C. E. Childs and associates for the microanalyses, and Dr. J. M. Vandenbelt and coworkers for determination of the spectral data.

(38) Melting points (corrected) were taken on a Thomas–Hoover capillary melting point apparatus.

(39) Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

Coumarin Derivatives as Coronary Vasodilators

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Received December 22, 1969

Many naturally occurring coumarin compounds have been shown to possess strong coronary vasodilating activity (visnadin, samidin, and dihydrosamidin).[1,2]

(1) T. O. Soine, *J. Pharm. Sci.*, **53**, 231–261 (1964).

(2) T. M. Blake, E. G. Wood, D. O'Moore, and R. G. Neel, *Amer. J. Med. Sci.*, **243**, 598 (1962).

TABLE I

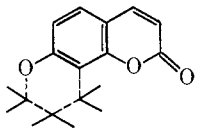
Compd	R_1 / N—R_2	Mp, °C	Yield, %	Recrystn solvent	Formula	Analysis
3	$N(C_2H_5)_2$	200[b]	45	Me_2CO–EtOH	$C_{21}H_{32}N_2O_3 \cdot 2HCl$	C, H, Cl, N
4	C_4H_8NO	260[b,c]	50	MeOH–EtOH	$C_{21}H_{30}N_2O_4 \cdot 2HCl$	C, H, Cl, N, O
5	$C_5H_{10}N$	270[b,c]	40	Me_2CO–MeOH	$C_{22}H_{32}N_2O_3 \cdot 0.5H_2O \cdot 2HCl$	C, H, Cl, N, O
6	4-C_6H_5–$C_4H_8N_2$[a]	180–182	60	MeOH–DMF	$C_{27}H_{35}N_3O_3$	C, H, N
7	C_4H_8N	190–192[b]	50	MeOH	$C_{21}H_{30}N_2O_3 \cdot 2HCl$	C, H, Cl, N, O
8	4-(2-$OCH_3C_6H_4$)$C_4H_8N_2$[a]	152–154	65	MeOH–EtOH	$C_{28}H_{37}N_3O_4$	C, H, N
9	3-CH_3–C_5H_9N	240[b]	40	EtOH	$C_{23}H_{34}N_2O_3 \cdot 2HCl$	C, H, N
10	$N(C_3H_7)_2$	225–227[b]	45	EtOH	$C_{23}H_{36}N_2O_3 \cdot 2HCl$	C, H, N
11	4-HO–H_2C–H_2C–$C_4H_8N_2$[a]	119	50	EtOH	$C_{22}H_{33}N_3O_4$	C, H, N

[a] 4-Substituted piperazinyl. [b] Dihydrochloride salt. [c] The synthesis of these compounds was disclosed by Cassella Farbwerke Mainkur Aktiengesellschaft to the author in a private communication after the above studies were complete.

TABLE II

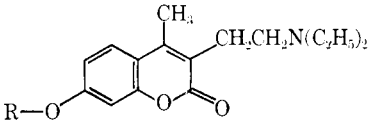
Compd	Dosage, mg/k	pO_2 Change percentage	pO_2 Duration (min)	Blood pressure Change mm Hg	Blood pressure Duration (min)	Heart rate Change percentage	Heart rate Duration (min)
Intensain	2	50	60	−5	60	2	60
3	10	0	0	0	0	0	0
4	10	0	0	0	0	0	0
5	10	−15	8	−10	5	16	5
6	5	52	4	7	31	−21	30
7	10	24	15	2	20	6	20
8	2	6	10	−20	10	4	10
9	7.2	−7	60	0	0	0	0
10	2	−57	5	0	0	0	0
11	10	19	36	0	0	0	0

The common characteristic feature of these compounds is the 7-oxycoumarin skeleton as in **1**. Recently a



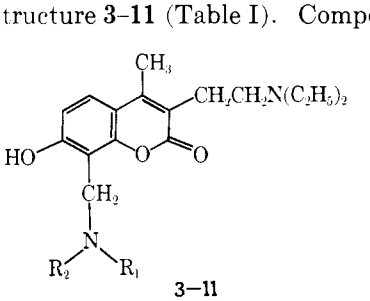
1

synthetic 7-hydroxy coumarin derivative, 3-β-diethylaminoethyl-4-methylcoumarin-7-ethyloxyacetate·HCl (II, R = $CH_2COOC_2H_5$) has been introduced as an antianginal drug.[3,4]



2

The present report includes the synthesis and evaluation of substituted 7-OH coumarin Mannich bases of the general structure **3–11** (Table I). Compounds **3–11**



3–11

are synthesized by refluxing an alcoholic solution of equimolar amounts of 3-β-diethylaminoethyl-4-methyl-7-hydroxycoumarin (**2**, R = H), paraformaldehyde and a secondary amine.

By analogy with previous work in this area,[5,6] the Mannich reaction is assumed to result in substitution on the 8 position of **2**.

Pharmacology.—The compounds recorded in Table I were injected in the jugular vein of anesthetized dogs at doses of 2–10 mg/k. The change in the oxygen tension of the coronary sinus blood (pO_2), heart rate and blood pressure were recorded by a procedure described by Schoepke, *et al.*[7] (Table II). A compound possessing good coronary vasodilating activity should cause an increase in pO_2 for extended periods with minimal effects on heart rate and blood pressure.[8]

4-Substituted piperazine Mannich bases, **6**, **8**, and **11**, and pyrrolidine Mannich base **7** of **2** (R = H) showed an increase in pO_2. 4-Aryl and substituted arylpiperazine Mannich bases, **6** and **8**, affected the heart rate and blood pressure significantly as compared to 4-β-hydroxyethylpiperazine Mannich base **11**. Compounds **7** and **11** showed an appreciable increase in pO_2 with minor or no effect on heart rate and blood pressure, but the duration of the increased pO_2 was too short (relative to the effect of II, R = CO_2Et) to warrant further investigation.

(3) A. C. Sonntag *Annu. Rep. Med. Chem. 1967*, 71 (1968).

(4) (Intensain®) Cassella Farbwerke Mainkur A.G., U.S. Patent 3,259,635 (1966); *Chem. Abstr.*, **59**, 11438 (1963).

(5) P. Dare, L. Verlicchi, and I. Setniker, *J. Org. Chem.*, **25**, 1097 (1960).

(6) V. N. Gupta, B. R. Sharma, and R. B. Arora, *J. Sci. Indian Res. Sect. B*, **20**, 300 (1961).

(7) H. G. Schoepke, T. D. Darby, and H. D. Brondyk, *Pharmacologist*, **8**, 204 (1966).

(8) Von P. Heistracher, O. Kraupp, and G. Spring, *Arzneim. Forsch.*, **14**, 1098 (1964).

Experimental Section[9]

Synthesis of Compounds 3–11.—Paraformaldehyde (0.01 mol) and a secondary amine (0.01 mol) were refluxed in EtOH solution for 2 hr. The intermediate **2** (R = H) (0.01 mol) was then added to the reaction mixture and refluxing was continued for 6–8 hr. The solvent was evaporated and the residue, if solid, was recrystallized. Bases which did not crystallize were converted into the dihydrochloride salts by treatment in Et_2O with dry HCl. For physical data, see Table I.

Acknowledgments.—The author wishes to express his appreciation to Dr. T. Darby, Mr. L. Wiemeler, and Mr. C. Shannon of the Pharmacology Department of Abbott Laboratories, North Chicago, Ill., for pharmacological investigations and permission to use their data.

[9] All melting points were taken with the Thomas–Hoover capillary melting point apparatus. Microanalyses were performed at the Microanalytical Laboratories of Abbott Laboratories, North Chicago, Ill. Ir spectra were recorded on a Beckman IR-8 infrared spectrophotometer.

Antimalarials. Antagonists of Pantothenic Acid[1]

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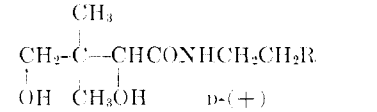
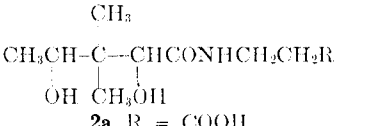
The antimalarial activity of some pantothenic acid antagonists (**1b,c,d**) is well documented.[2,3] However, at the time the antimalarial activity of **1b** was discovered, it was observed that the only analogs that acted as pantothenic acid antagonists were those which retained unchanged the pantoic acid portion (*i.e.*, $HOCH_2C(CH_3)_2CHOHCOOH$) of the pantothenic acid (**1a**). Since then this has been found to be incorrect. ω-Methylpantothenic acid (**2a**) is in fact the most inhibiting analog of pantothenic acid. Similarly ω-methylpantoyltaurine (**2b**) is more inhibitory than pantoyltaurine.[4] It was therefore considered of interest



D-(+)

1a, R = COOH **1c**, R = $SO_2NHC_6H_5$
b, R = COC_6H_5 **d**, R = SC_6H_5, SOC_6H_5, $SO_2C_6H_5$



2a, R = COOH
b, R = SO_3H

to test variously substituted amides of pantoyltaurine[5] (**10**) and ω-methylpantoyltaurine (**9**) as potential antimalarials. The compounds were synthesized according to Scheme I.

The variously substituted sulfamoylethylphthalimides (**5**, Table I) and the corresponding 2-aminoethanesulfonamides (**6**, Table II) were conveniently synthesized by following the previously described procedure for such compounds.[5] Although most of the amides of pantoyltaurine (**10**, Table IV) were obtained by the direct condensation of **6** with D-(−)-pantolactone (**8**) without solvent,[6] the same procedure failed in the synthesis of **9** (Table III). They were successfully obtained, however, by heating a mixture of the K salt of the sulfonamides **6** with the lactone **7** in a melt at 115–120°. A similar method was used in the preparation of **10** (**f**, **g**, **h**). The final compounds **9** and **10** were obtained as crystals only after great difficulty, usually following chromatography and then standing for days. Similar to the experience of Winterbottom, *et al.*,[5] we have found these compounds to have a pronounced tendency to form supersaturated solutions or to separate as oils even when seeded and cooled slowly.

Biological Results.—The compounds were screened for potential antimalarial activity in mice[6] infected with *Plasmodium berghei* and chicks[7] with *P. gallinaceum* by subcutaneous administration in a single dose. They were also evaluated against blood induced *P. gallinaceum* infections in mosquitoes[8] (*Aedes aegypti*).

None of the compounds submitted were considered active at the 640 mg/kg dose level. Even the lead compound from the World War II program, *i.e.*, **10**, R = *p*-C_6H_4Cl, is inactive in the present chick screen.[9] In our opinion the nonreproducibility of its activity lies in the present test procedure as the drug-diet method[10] was used before.

A few of the compounds were also tested by Dr. Trager in his *in vitro* system with *P. coatneyi* in monkey erythrocyte suspension, in a medium containing calcium pantothenate.[11] Compound **9b** was found to be as active as **10** (R = *p*-C_6H_4Cl) and **10f** much more active than the latter.

Experimental Section[12]

Melting points were obtained in capillaries and are uncorrected. Elemental analyses were performed by Spang Microanalytical Laboratories and Galbraith Laboratories, Inc. The uv, ir, and nmr spectra were as expected for the assigned structures.

2-Phthalimidoethanesulfonyl chloride (**4**) was prepared according to the procedure of Winterbottom, *et al.*[5] mp 160–162°.

(1) This investigation was supported by the U.S. Army Medical Research and Development Command Contract No. DA-49-193-MD-2879. This paper is Contribution No. 722 from the Army Research Program on Malaria and was the subject of a preliminary report at the First Northeast Regional Meeting of the American Chemical Society, Boston, Mass., Oct 1968.

(2) (a) F. Y. Wiselogle, "A Survey of Antimalarial Drugs, 1941–1945," Vol. I, J. W. Edwards, Ann Arbor, Mich., 1946, p. 250; (b) ref 2a, p 174; see also pp 138–140.

(3) For leading references and biological rationale see E. F. Elslager, M. P. Hutt, and L. M. Werbel, *J. Med. Chem.*, **11**, 1071 (1968).

(4) (a) W. Drell and M. S. Dunn, *J. Amer. Chem. Soc.*, **68**, 1868 (1946); (b) *ibid.*, **70**, 2058 (1948); (c) *ibid.*, **76**, 2804 (1954).

(5) R. Winterbottom, J. W. Clapp, W. H. Miller, J. P. English, and R. O. Roblin, *J. Amer. Chem. Soc.*, **69**, 1393 (1947).

(6) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

(7) Chicks (9–12 days old) were infected (intravenously) with a standard inoculum to produce a disease fatal to 100% of untreated controls within 3–4 days. Candidate compounds were dissolved or suspended in peanut oil and administered either subcutaneously or *per os* immediately after infection. A 100% increase in survival time was considered to be the minimum effective response to the antimalarial activity of the drug. Chicks surviving 30 days are recorded as cures.

(8) E. J. Gerberg, L. T. Richards, and J. B. Poole, *Mosquito News*, **26**, 359 (1966).

(9) Personal communication from Drs. Strube and B. Poon of WRAIR.

(10) Reference 2, p 491; test procedure 0-1.

(11) W. Trager, *Trans. N. Y. Acad. of Sci.*, **28**, 1094 (1966).

(12) Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.