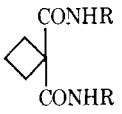
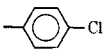
TABLE I: DIAMIDES OF CYCLOBUTANE-1,1-DICARBOXYLIC ACID



No.		Yield, %	Mp, °C[a]	Crystn solvent[b]	Formula	Analyses	Gross effect[c]	R'[d]
1	CH_3	50	204	A	$C_8H_{14}N_2O_2$	N	S	1.1
2	$(CH_2)_2CH_3$	56	145	A	$C_{12}H_{22}N_2O_2$	N	S	8.8
3	$(CH_2)_5CH_3$	50	79	P	$C_{18}H_{34}N_2O_2$	N	S	1.9
4	$CH(CH_3)_2$	40	195	A	$C_{12}H_{22}N_2O_2$	N	S	2.3
5	$C(CH_3)_3$	45	195	P	$C_{14}H_{26}N_2O_2$	N	S	2.3
6		70	212	A	$C_{18}H_{30}N_2O_2$	N	N	1.2
7		65	232	A	$C_{20}H_{34}N_2O_2$	N	N	0.9
8		75	258	A	$C_{18}H_{16}Cl_2N_2O_2$	N	N	1.2

[a] Corrected. [b] A, acetone; P, pentane. [c] Drug dose was 1000 mg/kg orally. N = no effect, S = slight reduction in spontaneous motor activity, subjectively graded and compared with control animals receiving medium only. [d] Drug dose was 500 mg/kg orally. R' = (drug + pentobarbital sleep time)/(pentobarbital sleep time). Pentobarbital dose, 50 mg/kg ip administered 30 min after test drug.

true potentiation and becomes significant when greater than 1.5. The fact that **1** is active as a depressant but inactive as a barbiturate potentiator lends some support to the suggestion that there is functional independence of sites for the two types of activity.[3]

Two of the compounds, **1** and **2**, were also tested for anticonvulsant[6] (pentylenetetrazole antagonism), antistrychnine lethality,[7] and antitremorine[8] effects.[3] Neither showed antagonism to pentylenetetrazole- or strychnine-induced convulsions. However, they completely protected 40–60% of the test animals from tremorine-induced tremors at an oral dose of 1000 mg/kg.

Experimental Section

Microanalyses were performed by Midwest Microlab Inc., Indianapolis, Ind. Where analyses are indicated only by elemental symbols, analytical results for those elements were within ±0.4% of theoretical values.

Preparation of Diamides.—The methods used in synthesizing diamides of cyclobutane-1,1-dicarboxylic acid were essentially the same as those reported for producing diimides of that acid.[1] Crystallization solvents and yields are reported in Table I.

Acknowledgments.—This work was made possible by research Grant NB-7548 of the National Institutes of Health, U. S. Public Health Service.

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Substituted Chromones as Coronary Vasodilators

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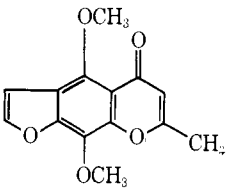
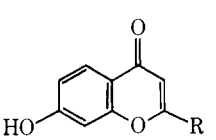
Khellin or 2-methyl-5,8-dimethoxyfuranochromone (I) and some of its analogs are known to be coronary vasodilators.[1-3] This paper describes the synthesis and pharmacological properties of a number of new substituted chromones (III–XII) which were prepared as potential coronary vasodilators (Table I). In addition to the fact that III–XII share the characteristic features of active chromones,[2,3] these compounds could also be considered khellin analogs in which the furane ring of the khellin molecule (I) is not a part of the rigid furanochromone structure, but instead is attached to the chromone molecule through an ether linkage as in VI, VII, and XI.



I

Chemistry.—2-Furyl-7-hydroxychromone (II, R = 2-furyl) was synthesized from 2,4-dihydroxyacetophenone and 2-furoyl chloride by a standard three-step procedure.[4] The synthesis of 2-aryl-7-hydroxychromones (II, R = C_6H_5 and $C_6H_4OCH_3$-4) is already described in the literature.[5]



II

The chromones II (R = C_6H_5, $C_6H_4OCH_3$-4, and 2-furyl) were treated with various chloromethyl intermediates and acid chlorides to give the desired compounds III–XII.

(1) R. Charlier, "Coronary Vasodilators," Pergamon Press Inc., New York, N. Y., 1961, p 84.
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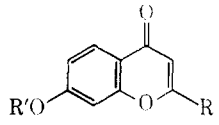
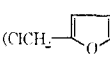
(4) D. Donnelly, R. Geoghegan, C. O'Brien, E. Phillin, and T. S. Wheeler, *J. Med. Chem.*, **8**, 872 (1965).
(5) W. Baker, *J. Chem. Soc.*, 1381 (1933).

TABLE I



Compd no.	R	R'	Recrystn solvent	Yield, %	Mp, °C	Formula	Analyses	Pharmacological data: Dose, mg/kg	PO_2 % change	Duration, min
III	2-Fu	$CH_2CO_2C_2H_5$	DMF–MeOH	50.5	155–157	$C_{21}H_{14}O_6$	C, H, O	10	−8	5
IV	2-Fu	$(CH_2)_2N(C_2H_5)_2$	EtOH–Me_2CO	42.5	218–220	$C_{19}H_{22}ClNO_4$	C, H, Cl, N, O	10	−4	4
V	2-Fu	2-COFu	Me_2CO	60.6	168–170	$C_{18}H_{10}O_6$	C, H, O	2	0	0
VI[a]	2-Fu	2-CH_2Fu-5-$CO_2C_2H_5$	DMF–MeOH	40.8	180	$C_{23}H_{16}O_7$	C, H, O	2	+11	3
VII[a]	C_6H_5	2-CH_2Fu-5-$CO_2C_2H_5$	DMF–MeOH	45.0	168	$C_{23}H_{18}O_5$	C, H, O	10	−5	8
VIII	C_6H_5	2-COFu	DMF–EtOH	60.5	167–168	$C_{20}H_{12}O_5$	C, H, O	10	0	0
IX	C_6H_5	$(CH_2)_2OC_6H_5$	EtOH	50.8	162	$C_{25}H_{18}O_4$	C, H, O	10	−40	3
X	4-$C_6H_4OCH_3$	2-COFu	DMF–MeOH	70.3	195	$C_{20}H_{14}O_6$	C, H, O	10	−9	11
XI[a]	4-$C_6H_4OCH_3$	2-CH_2Fu-5-$CO_2C_2H_5$	DMF–MeOH	50.3	165	$C_{25}H_{20}O_7$	C, H, O	2	−9	10
XII	2-Fu	$OCC_6H_4(OCH_3)$s-3,4,5	DMF–MeOH	70.0	215	$C_{24}H_{16}O_7$	C, H, O	10	+19	8

[a] The intermediate ethyl 5-(chloromethyl)-2-furoate () used in the synthesis of these compounds was prepared according to a known procedure: A. L. Mndzhoian, "Synthesis of Heterocyclic Compounds", Vol. 1 and 2, Consultants Bureau, Inc., New York, N. Y., 1959, p 29.

Pharmacology.—It was presumed that coronary vasodilating activity of III–XII will cause an increase in PO_2 as measured in the coronary sinus. The compounds were injected into the jugular vein of anesthetized dogs at doses of 2 and 10 mg/kg and the effect on the oxygen tension of the coronary sinus blood (PO_2) was measured by essentially the same method as described by Schoepke, *et al.*[6] The data described in Table I show that only VI and XII showed a slight increase in PO_2, but it was not sufficient to be of any further interest.

Experimental Section[7]

Synthesis of 2-(2-Furyl)-7-hydroxychromone (II, R = 2-Fu). 2′,4′-Dihydroxyacetophenone Difuroate.—2-Furoyl chloride (26.0 g, 0.20 mole) in dry PhH (80 ml) was added gradually to a well-stirred ice-cold solution of 2,4-dihydroxyacetophenone (15.20 g, 0.1 mole) in pyridine (70 ml). After 24 hr the mixture was added to excess dilute HCl. The product, which separated, crystallized from EtOH; yield 39.10 g (70%), mp 115–116°. *Anal.* ($C_{18}H_{12}O_7$) C, H, O.

1-(2,4-Dihydroxyphenyl)-3-(2-furyl)-1,3-propanedione-4-(2-furoate).—Powdered KOH (2.0 g) was added to a solution of 2′,4′-dihydroxyacetophenone difuroate (5.0 g) in dry pyridine (75 ml). The mixture was shaken vigorously for 15 min and set aside for 12 hr. The crude product, liberated by the addition of cold dilute AcOH, was washed with H_2O. It crystallized (Me_2CO) in yellow needles, yield 1.3 g (25%), mp 154°. *Anal.* ($C_{18}H_{12}O_7$) C, H, O.

2-(2-Furyl)-7-hydroxychromone (II, R = 2-Fu).—1-(2,4-Dihydroxyphenyl)-3-(2-furyl)-1,3-propanedione-4-(2-furoate) (1.0 g) was dissolved in concentrated H_2SO_4 (5 ml) and set aside for 4 hr at room temperature. It was poured onto crushed ice and neutralized with 10% NaOH. The product which separated crystallized from DMF and MeOH mixture; yield 0.2 g (25%), mp 320–325°. *Anal.* ($C_{13}H_8O_4$) C, H, O.

{[2-(2-Furyl)-4-oxo-4H-1-benzopyran-7-yl]oxy}acetic Acid Ethyl Ester (IX).—A mixture of 4.6 g (0.02 mole) of II (R = 2-Fu) and 4.0 g of K_2CO_3 in 100 ml of MeCOEt was refluxed with stirring at 70° for 1 hr. Then 2.44 g (0.02 mole) of ethyl chloroacetate was added dropwise. The reaction mixture was stirred under reflux for 9 hr. The hot reaction mixture was filtered with suction and the filtrate was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and the solution was washed several times with dilute NaOH and finally with H_2O. The CH_2Cl_2 solution was concentrated *in vacuo* to dryness. The residue was recrystallized from a mixture of DMF–MeOH; mp 155–157° (see Table I, III for physical data). Compounds IV, VI, VII, IX, and XI were synthesized by the same method as III from various 2-substituted 7-OH chromones and chloromethyl intermediates.

2-(2-Furyl)-7-hydroxychromone 2-Furoate (Table I, V).—To a solution of 4.6 g (0.02 mole) of II (R = 2-Fu) in 50 ml of dry C_5H_5N was added dropwise 2.6 g (0.02 mole) of 2-furoyl chloride. The mixture was stirred at room temperature for 24 hr. The crude product, liberated by the addition of dilute HCl, was recrystallized from Me_2CO; mp 168–170° (see Table I, V for physical data). VIII, X, and XII were synthesized by the same procedure as V.

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

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(7) Melting points were determined with the Thomas–Hoover capillary melting point apparatus. Microanalyses were prepared at the Microanalytical Laboratories of Abbott Laboratories, North Chicago, Ill.

N-[3-(1-Alkylpiperidyl)]acetamides and N,N-Dimethyl-N′-[3-(1-alkylpiperidyl)]ureas as Cholinesterase Inhibitors. I

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Previous investigations by Lasslo,[1] Beasley,[2] Quintana,[3] Purcell[4] and their coworkers have involved studies of the effects of 3-(1-alkylpiperidyl)carbox-

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