the clear mother liquor, petroleum ether (100 mL, bp 30–60 °C) was added and the solution was refrigerated overnight. The solid was filtered and recrystallized from $CHCl_3$–petroleum ether to yield the title compound (2.4 g, 36%): mp 240–243 °C (with shrinking and darkening ~200 °C); NMR (DMF-d_7) δ 10.13 (s, 1 H), 7.63 (s, 8 H), 5.13 (s, 2 H).

3-Methyl-5,5-bis(4-chlorophenyl)hydantoin (7). 5,5-Bis-(4-chlorophenyl)hydantoin (6 g, 0.0187 mol) was suspended in a solution of sodium hydroxide (0.8 g, 0.02 mol) in water (80 mL) and stirred until a clear solution was obtained. Dimethyl sulfate (10 mL, 0.103 mol) was added to the above solution (with vigorous stirring). After 4 h, the solid product was filtered, washed with water, and recrystallized from ethanol to give 5.2 g (83%) of white crystals: mp 248–250 °C; NMR (Me_2SO-d_6) δ 10.05 (s, 1 H), 7.57 (s, 8 H), 3.03 (s, 3 H).

1,3-Dichloro-5-methyl-5-(2-thienyl)hydantoin (15). To a solution of **10** (4.0 g, 20.2 mmol) in 0.1 N NaOH (420 mL, 42.0 mmol) was added chlorine water (400 mL, 44.0 mmol). The precipitate was collected, dried, slurried with carbon tetrachloride (50 mL), and filtered to give 3.1 g (55%) of the title compound, mp 100–103 °C.

3,5-Dimethyl-5-(2-thienyl)hydantoin (16). Compound **10** (5.0 g, 25.5 mmol) and dimethyl sulfate (3.3 g, 26 mmol) were added to a sodium methoxide solution prepared from sodium (600 mg, 0.026 g-atom) and methanol (100 mL). The solution was refluxed for 2 h, cooled, and filtered to give the title compound (4.8 g, 90%), mp 182–185 °C.

5,5-Bis(2-thienyl)hydantoin (20). Di(2-thienyl) ketone (23.2 g, 0.12 mol) in dimethylformamide (120 mL), potassium cyanide (10 g, 0.15 mol) in water (24 mL), ammonium carbonate (46.1 g, 0.48 mol), and urea (10.8 g, 0.18 mol) were heated in an autoclave at 135 °C for 36 h. The reaction mixture was poured into water (600 mL) and acidified. The resulting solid was collected, slurried in 5% sodium hydroxide, and refiltered to give 14.5 g of recovered starting material. The basic mother liquor was charcoaled and acidified to give the title compound (7.96 g, 25%), mp 216–219 °C. The analytical sample was prepared by recrystallization from acetone–water. The melting point was unchanged.

5,5-Spiro(3,4-dithiacyclopentyl)hydantoin (27). 5,5-Bis-(benzylthiomethyl)hydantoin (**26**)[11] (12.0 g, 33.2 mmol) was dissolved in liquid ammonia (700 mL) at −70 °C. Sodium (3.20 g, 0.139 g-atom) was added in small pieces until the blue color remained. Excess sodium was destroyed with ammonium chloride and the mixture was evaporated to dryness. The residue was dissolved in water (150 mL) and acidified with concentrated hydrochloric acid (20 mL). The solution was extracted with benzene (once) and with ethyl acetate (four times). The combined ethyl acetate extract was dried (Na_2SO_4) and evaporated below 40 °C to give 4.1 g (65%) of crude the 5,5-bis(mercaptomethyl)hydantoin intermediate. This was dissolved in ethanol (350 mL) and added dropwise to 0.2 N aqueous iodine (250 mL). Excess iodine was destroyed ($Na_2S_2O_3$) and the solution was evaporated to ca. 100 mL. Upon cooling, the product crystallized. Recrystallization from ethanol gave the title compound (1.6 g, 40%), mp 241–244 °C dec.

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References and Notes

(1) Compound **2** was tested some 15–20 years ago as NSC 23306 (C. L. Stevens and C. H. Chang, Wayne State University) and received limited clinical testing. Adverse characteristics of **2** were its very low solubility in water as well as its reactivity toward oxidizable vehicles. More recently (early 1970), the compound was retested as NSC 152498 and, as stated in the text, gave T/C values against P-388 lymphocytic leukemia as high as 190% with good dose–response characteristics.
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Antiallergic Agents. Xanthone-2,7-dicarboxylic Acid Derivatives

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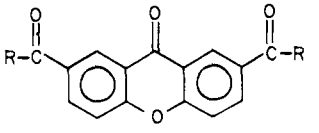
Xanthone-2,7-dicarboxylic acid (1), a known inhibitor of the rat passive cutaneous anaphylaxis (PCA) assay by the iv route, was found to lack oral activity. Conversion of 1 into bis(carboxamide) derivatives afforded orally active compounds.

An orally effective antiallergic agent possessing a mode of action similar to that of disodium cromoglycate[1,2] would be most welcome in the treatment of certain allergic conditons. Pfister et al.[3] reported that xanthone-2-carboxylic acid derivatives were effective in the rat passive cutaneous anaphylaxis (PCA) assay by the iv route and that 7-propyl and 7-propoxy substitution afforded orally active compounds. They reported that xanthone-2,7-dicarboxylic acid (1) was active by the iv route. We were interested in 1 as a potential antiallergic agent and ob-

Table I. Physical Properties and Activities in the Rat Passive Cutaneous Anaphylaxis (PCA) Assay of Xanthone-2,7-dicarboxylic Acid Derivatives



No.	R	Mp, °C	Yield, %	Mol formula[a]	Recrystn solvent	% inhibn, PCA wheal area, 100 mg/kg po, 1 h[b]	p values
1	OH	>360	70	$C_{15}H_8O_6$	DMF	1.0	
2	OCH_2CH_3	168–170	75	$C_{19}H_{16}O_6$	EtOH	8.0	
3	NH_2	>325	55	$C_{15}H_{10}N_2O_4$[c]	CF_3CO_2H-H_2O	34	0.01
4	$NHCH_3$	>300	41	$C_{17}H_{14}N_2O_4$	DMF-H_2O	19	>0.1
5	NHC_3H_7	274–277	79	$C_{21}H_{22}N_2O_4$	MeOH-H_2O	19	>0.1
6	$NH(CH_2)_3OCH_2CH_2OCH_3$	145–158	73	$C_{27}H_{34}N_2O_8$	CH_2Cl_2-heptane	19	0.1
7	$N(CH_3)_2$	220–222	68	$C_{19}H_{18}N_2O_4$	MeOH-H_2O	69	<0.001
8	$N(CH_2CH_3)_2$	74–78	56	$C_{23}H_{26}N_2O_4 \cdot C_6H_5CH_3$[d]	Toluene	53	<0.01
9	$N(c\text{-}C_6H_{11})_2$	248–250	39	$C_{39}H_{50}N_2O_4$	$CHCl_3$-heptane	42	0.01
10	$N(CH_2CH{=}CH_2)_2$	85	63	$C_{27}H_{26}N_2O_4$	MeOH-H_2O	51	<0.001
11	$c\text{-}NC_5H_{10}$	185–187	94	$C_{25}H_{26}N_2O_4$	CH_2Cl_2-heptane	57	<0.001
12		239–241	5	$C_{31}H_{34}N_2O_4$	MeOH-H_2O	48	<0.001
13	$c\text{-}N(CH_2CH_2)_2O$	248–250	39	$C_{23}H_{32}N_2O_6$	$CHCl_3$-heptane	42	0.01

[a] Melting points were determined in open capillaries and are uncorrected. Compounds were routinely examined by NMR, IR, and UV, and their spectra were consistent with the proposed structures. All compounds were analyzed for C, H, and N and were within ±0.4% of the theoretical value unless otherwise stated. [b] See biological methods for experimental details. [c] N: calcd, 9.92; found, 9.25. [d] Analyzed and tested as the toluene solvate.

served that it was active ip but inactive po. This paper is concerned with the derivatization of 1 to yield bis(carboxamides) that were orally active in the rat PCA assay.

The compounds in Table I were synthesized by standard methods starting with xanthone-2,7-dicarbonyl chloride[4] derived from 1 and were evaluated in the rat PCA assay originally described by Mota.[5] Compounds were given orally at a standard dose of 100 mg/kg 1 h before challenge.

Structure–activity comparisons of the acid 1, ester **2**, and primary amide 3 revealed that oral activity was associated with the amide while the ester and acid were devoid of activity by the oral route. With this information in hand, we attempted to maximize the activity within the amide series. The secondary amides **4–6** were consistently less active than **3** while the tertiary amides **7–13** were generally more potent than **3**.

The most potent compound in the series, on a weight basis, was **7**, which inhibited the wheal reaction by 69%. When the data for the tertiary amides were compared on a molar basis, however, the activities were much closer to each other than indicated by the data in Table I. For example, **7** has a molecular weight of 338.35 and the administered dose of 100 mg/kg was equivalent to 0.30 mM whereas **9** with a molecular weight of 610.81 was administered at a dose of 0.16 mM. The latter compound administered at approximately one-half the molar dose produced a response equal to 60% of **7**. These results would suggest that the SAR for the tertiary amides was rather nonspecific relative to the steric and lipophilic properties of the inhibitor. In summary, this work has shown that conversion of xanthone-2,7-dicarboxylic acid to bis(carboxamides) introduced oral activity into a previously orally inactive structure.

Experimental Section

Biological Methods. Male Sprague–Dawley rats weighing 200–250 g were used in these studies. Groups of eight animals per drug were employed. A volume of 0.1 mL of a 1:8 dilution of homocytotropic antiovalbumin antiserum was injected intradermally 48 h prior to challenge. The challenge consisted of an intracardiac injection of the specific antigen, 30 mg of ovalbumin in 0.5 mL of physiologic saline, mixed with an equal amount of 1% Evans blue dye. The dye was used to make the wheal more visible. Compounds were administered at a dose of 100 mg/kg po 1 h before challenge. Control rats were given the vehicle H_2O at 1 mL/100 g of body weight. Rats were sacrificed 20 min after challenge. Diameters of wheals on reflected skin were measured in millimeters and converted to areas in square millimeters.

Chemistry. The amides and ester were prepared by standard methods. In a typical example, diallylamine (16.60 g, 0.2 mol) was added dropwise to a warm solution of xanthone-2,7-dicarboxylic acid chloride[4] (12.84, 0.04 mol) in $CHCl_3$ (200 mL) over 15 min. The solution was stirred at room temperature for 2 h and concentrated in vacuo, and the residue was extracted with Et_2O. The Et_2O solution was filtered and concentrated in vacuo and the residue when recrystallized (MeOH–H_2O) gave 11.5 g (63%) of **8**, mp 85 °C. Anal. C, H, N.

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