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Benzopyrones. 7. Synthesis and Antiallergic Activity of Some 2-(5-Tetrazolyl)chromones[1]

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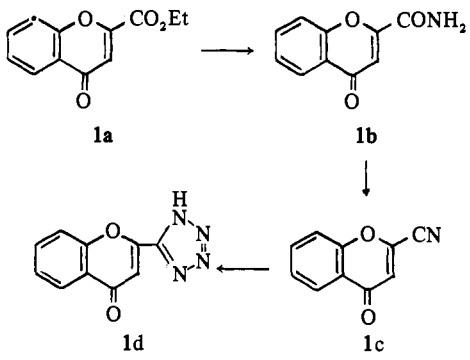
Antiallergic properties in the chromone series appear[2-4] to be largely confined to those compounds which contain a carboxyl group at C-2. Replacement of a carboxyl by a 5-tetrazolyl group in a biologically active carboxylic acid[5-8] has sometimes resulted in retention of activity but rarely in an improvement in potency. This paper reports the synthesis and antiallergic properties of a number of chromones,[9] such as **1d** and its substituted derivatives, which carry a 5-tetrazolyl group at C-2. The variations in structure are shown in Table I.

Chemistry. The title compounds which are listed in Table II were prepared by the route shown in Scheme I.

Scheme I



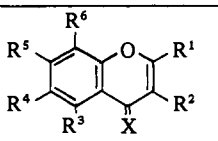
The carboxylic esters, prepared[14] from the appropriate 2-hydroxyacetophenone and diethyl oxalate, reacted with gaseous NH_3 at 0° to give high yields of the carboxamides. Although several carboxamides of this kind are known, their dehydration to the 4-oxo-4*H*-1-benzopyran-2-carbonitriles has not been reported. The unsubstituted carbonitrile **1c**, the only known member of this series, was synthesized[12] in five stages from 2-methylchromone *via* the 2-carboxaldehyde. A more convenient method is now described through the dehydration of the carboxamide by means of an arylsulfonyl chloride and pyridine in DMF. Other reagents,[19] such as $POCl_3$, PCl_5-$POCl_3$, $SOCl_2$, or P_2O_5, proved to be ineffective while benzenesulfonyl chloride in pyridine[20] gave a low yield. 3-Chloro-4-oxo-4*H*-1-benzopyran-2-carbonitrile (**17c**) was prepared by reacting the unsubstituted nitrile (**1c**) with sulfuryl chloride.

The carbonitriles were converted smoothly to the tetrazoles by reaction with sodium azide and ammonium chloride in DMF.[21] A recent study[22] showed that the pK_a of 4-oxo-4*H*-1-benzopyran-2-carboxylic acid was 2.96. The low solubility of the corresponding tetrazole (**1d**) in water and ethanol caused difficulties in the accurate determination of its pK_a but, using a potentiometric method, a value (2.8) was obtained which showed that the acidity of both carboxylic acid and tetrazole are comparable.

Biological Results. The tetrazoles were screened for antiallergic activity in rats by means of the passive cutaneous anaphylaxis test using an extract of *Nippostrongylus brasiliensis* as antigen[23] and disodium cromoglycate as standard. Those compounds which showed activity comparable with or better than disodium cromoglycate are listed in Table III. Although the nature of the test makes it difficult to quantify the results, **1d**, **3d**, **4d**, and **14d** are appreciably more potent than the standard drug. Substitution by alkyl or halogen at C-3 or C-8 lowers activity as does the replacement of the 4-oxo by 4-thioxo group. The activity level is very susceptible to comparatively small changes in the substituents at C-7 (*cf.* **4d**, **12d**, and **13d**). This study shows that a carboxyl group in chromone-2-carboxylic acids may be advantageously replaced by a tetrazolyl group which confers a comparable degree of acidity on the molecule.

Four compounds, **2b**, **2c**, **9d**, and **14b**, showed activity similar to aspirin in reducing writhing induced by phenylquinone[24] but were almost inactive in the hot plate test.[25] The oral LD_{50} values of all the compounds in mice were greater than 100 mg/kg.

Table I. Substituted Chromones Synthesized



a, $R^1 = CO_2Et$
b, $R^1 = CONH_2$
c, $R^1 = CN$
d, R^1 = 5-tetrazolyl

Compd No.	R^2	R^3	R^4	R^5	R^6	X
1	H	H	H	H	H	O
2	Me	H	H	H	H	O
3	H	H	Me	H	H	O
4	H	H	H	Me	H	O
5	H	H	H	H	Me	O
6	H	Me	H	Me	H	O
7	H	H	Cl	H	H	O
8	H	H	Br	H	H	O
9	H	H	Br	H	Br	O
10	H	H	Me	H	Br	O
11	H	OMe	H	H	H	O
12	H	H	H	OMe	H	O
13	H	H	H	OCH_2Ph	H	O
14	H	H	NO_2	H	H	O
15	H	H	NO_2	H	Me	O
16	H	H	H	H	H	S
17	Cl	H	H	H	H	O

Experimental Section

Melting points were determined on a Reichert hot stage apparatus using a calibrated thermometer. A low value for the N content of a few tetrazoles was obtained although the combustion time was increased as recommended by the manufacturers of the instrument (Hewlett Packard).

General Method of Synthesis. (a) Ethyl 4-Oxo-4*H*-1-benzopyran-2-carboxylates. The esters were prepared by the method of Zagorevskii, *et al.*[14] The following new substituted 4-oxo-4*H*-1-benzopyran-2-carboxylic acids (from EtOH) were obtained from the esters by hydrolysis with a mixture of HCl and AcOH (analyzed for C and H): 8-methyl-, mp 272–273° dec; 5,7-dimethyl-, mp 251–252° dec;

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Table II. Chromones[a]

No.	a, R^1 = CO_2Et Mp, °C	Yield, %	Formula	b, R^1 = $CONH_2$ Mp,[b] °C	Yield, %	Formula	c, R^1 = CN Mp, °C	Yield, %	Formula	d, R^1 = 5-Tetrazolyl Mp,[b] °C	Yield, %	Formula
1	64–65[c]	66		256–257[d]	94		129–130[e]	74		270–271	88	$C_{10}H_8N_4O_2$[f]
2	90–91[g]	45		250–252	85	$C_{11}H_9NO_3$	145–146	88	$C_{11}H_7NO_2$	249–250	58	$C_{11}H_8N_4O_2$
3	78–80	73	$C_{13}H_{12}O_4$	325–329	93	$C_{11}H_9NO_3$	160–161	73	$C_{11}H_7NO_2$	273–274	87	$C_{11}H_8N_4O_2$[h]
4	57–58	72	$C_{13}H_{12}O_4$	322–323	96	$C_{11}H_9NO_3$	146–147	68	$C_{11}H_7NO_2$	275–276	80	$C_{11}H_8N_4O_2$[i]
5	100–101	82	$C_{13}H_{12}O_4$	285–287	86	$C_{11}H_9NO_3$	98–100	92	$C_{11}H_7NO_2$	264–265	93	$C_{11}H_8N_4O_2$
6	136–137	66	$C_{14}H_{14}O_4$	337–338	96	$C_{12}H_{11}NO_3$	145–146	74	$C_{12}H_9NO_2$	275–276	95	$C_{12}H_{10}N_4O_2$
7	136–137[j]	84		314–315	97	$C_{10}H_6ClNO_3$	204–206	65	$C_{10}H_4ClNO_2$	252–253	96	$C_{10}H_5ClN_4O_2$
8	143–144[k]	67		308–310	91	$C_{10}H_6BrNO_3$	200–201	75	$C_{10}H_4BrNO_2$	266–267	96	$C_{10}H_5BrN_4O_2$
9	134–135[l]	90		318–320	89	$C_{10}H_5Br_2NO_3$	160–161	65	$C_{10}H_3Br_2NO_2$	269–270	85	$C_{10}H_4Br_2N_4O_2$
10	143–144	74	$C_{13}H_{11}BrO_4$	298–300	82	$C_{11}H_8BrNO_3$	181–182	84	$C_{11}H_6BrNO_2$	272–273	74	$C_{11}H_7BrN_4O_2$
11	130–131[m]	59		284–285	91	$C_{11}H_9NO_4$	161–162	58	$C_{11}H_7NO_3$	256–257	66	$C_{11}H_8N_4O_3$
12	122–123[n]	73		298–300	97	$C_{11}H_9NO_4$	150–153	89	$C_{11}H_7NO_3$	265–267	71	$C_{11}H_8N_4O_3$
13	172–173[o]	81		280–282	97	$C_{17}H_{13}NO_4$	135–136	82	$C_{17}H_{11}NO_3$	235–237	61	$C_{17}H_{11}N_4O_3$
14	178–179[p]	86		256–257	97	$C_{10}H_6N_2O_5$	150–151	92	$C_{10}H_4N_2O_4$	256–257	92	$C_{10}H_5N_5O_4$[q]
15	172–173	90	$C_{13}H_{11}NO_6$	348–350	92	$C_{11}H_8N_2O_5$	164–165	95	$C_{11}H_6N_2O_4$	217–218	78	$C_{11}H_7N_5O_4$
16	101–103[r]	81		274–275	99	$C_{10}H_7NO_2S$	163–164	71	$C_{10}H_5NOS$	280–282	77	$C_{10}H_6N_4OS$
17	82–85[s]	67					161–162	63	$C_{10}H_4ClNO_2$	234–236	77	$C_{10}H_5ClN_4O_2$[t]

[a] Analytical results for C, H, and N (where present) were within ±0.4% of the theoretical value except for a few tetrazoles which gave slightly low N values (see footnotes *f*, *h*, *i*, *q*, and *t*). [b] Dec. [c] Lit.[10] mp 69–70°. [d] Lit.[11] mp 250–251°. [e] Lit.[12] mp 129–131°. [f] N: calcd, 26.2; found, 25.3. [g] Lit.[13] mp 93–94°. [h] N: calcd, 24.5; found, 23.8. [i] N: calcd, 24.5; found, 23.7. [j] Lit.[13] mp 136–137°. [k] Lit.[14] mp 143–144°. [l] Lit.[15] mp 134–135°. [m] Lit.[16] mp 130–131°. [n] Lit.[15] mp 122–123°. [o] Lit.[17] mp 172–172°. [p] Lit.[11] mp 178–179°. [q] N: calcd, 27.0; found, 26.3. [r] Lit.[18] mp 101–103°. [s] Lit.[11] mp 91–92°. [t] N: calcd, 22.5; found, 21.9.

Table III. Inhibition of Passive Cutaneous Anaphylaxis by 2-(5-Tetrazolyl)chromones

Compd No.	Route	Dose, mg/kg	Inhibitory act.[a]
1d	Iv[b]	1	+++
3d	Ip[c]	50	+++
4d	Iv	1	+++
5d	Iv	5	+
6d	Iv	1	++
7d	Iv	1	+
	Iv	5	+++
8d	Iv	1	+
	Iv	5	+++
12d	Ip	50	++
14d	Ip	50	+++
17d	Iv	1	+
Disodium cromoglycate	Iv	1	+
	Iv	5	+++
	Ip	50	++

[a] +, slight activity; ++, moderate activity; +++, marked activity. [b] Drug administered with the antigen. [c] Drug administered 15 min before antigen.

8-bromo-6-methyl-, mp 265–266° dec; higher mps were obtained for the following acids: 7-methyl-, mp 271–272° dec (lit.[13] 261°); 3-chloro-, mp 213–214° dec (lit.[11] 206°).

(b) **4-Oxo-4*H*-1-benzopyran-2-carboxamides. Method A.** The above esters, by reaction[26] in EtOH with gaseous NH_3 at 0° for 20 min gave the corresponding carboxamides.

Method B. 4-Oxo-4*H*-1-benzopyran-2-carboxamide **(1b)** was also prepared in 80% yield from the acid chloride which was prepared by the following modification of the method of Zagorevskii, *et al.*:[15] the carboxylic acid (0.13 mole), suspended in 1,2-dichloroethane (150 ml) and DMF (0.2 ml), was heated under N_2 under reflux for 3–4 hr with $SOCl_2$ (0.165 mole). The crude acid chloride (mp 95–98°, 90% yield), obtained by removing the excess of $SOCl_2$ and solvent under vacuum, was used immediately.

(c) **4-Oxo-4*H*-1-benzopyran-2-carbonitrile.** A mixture of the carboxamide (1 mole), benzene- or toluene-4-sulfonyl chloride (1.5 moles), pyridine (3 moles), and DMF (5 ml/g of carboxamide) was heated at 85–90° on an oil bath for 7–8 hr. After allowing to stand overnight, the mixture was poured into ice water, and the precipitated solid was collected to give the 2-carbonitrile (from aqueous EtOH).

(d) **2-(5-Tetrazolyl)chromones.** The carbonitriles were converted[21] into the tetrazoles by reaction with NaN_3 and NH_4Cl in DMF.

3-Chloro-4-oxo-4*H*-1-benzopyran-2-carbonitrile (17c). The carbonitrile **(1c)** (8.6 g, 0.05 mole), sulfuryl chloride (25 ml, 0.31 mole), and benzoyl chloride (0.1 g, 0.0007 mole) were refluxed for 10 hr. Removal of the excess sulfuryl chloride under vacuum gave **17c** (from aqueous EtOH).

Determination of the pK_a of the Tetrazole 1d. Using a potentiometric method,[27] the pK_a of **1d** in 50% aqueous EtOH at 20° was found to be 2.8.

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Photochemistry of Zearalenone and Its Derivatives

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In the course of studying the biological activity profile of zearalenone and several of its derivatives,[1,2] it seemed appropriate to examine the effect that molecular shape has on uterotropic activity.

From molecular models, it appeared that one of the most dramatic changes that could be made in the molecular shape was to convert the trans-1′,2′ double bond† in zearalenone to the cis arrangement. This cis-trans stereoisomerization can most easily be accomplished by a photochemical process.‡

Zearalenone (**1**) and each of the diastereomeric zearalenols (**3a, b**) were dissolved in methanol and irradiated until a photostationary state was reached. In each case, the photostationary state consisted of >97% of the cis isomer.

A comparison of the nmr spectra of **1** and **2** showed that the change in the chemical shift of the proton on C-1′, from δ 7.14 in **1** to 6.72 in **2**, along with the change in the coupling constant, $J_{1',2'}$, from 16 Hz in **1** to 11.5 Hz in **2**, clearly supported the cis assignment of stereochemistry about the carbon-carbon double bond in **2**. In addition, a number of other protons in the molecule had undergone shielding effects due to the change in molecular shape. For example, the signal for the proton on C-5 of the aromatic ring is shifted upfield by 18 Hz due to a shielding effect by the carbon-carbon double bond. Other upfield shifts by the allylic protons on C-3′ (42 Hz) and the protons on C-5′ and C-7′ (22 Hz) are probably due to the shielding effect by the aromatic π-electrons as a result of the 14-membered ring being folded over the shielding cone of the aromatic ring. Similar shielding effects were observed for each of the diastereomeric zearalenols (**4a, b**).

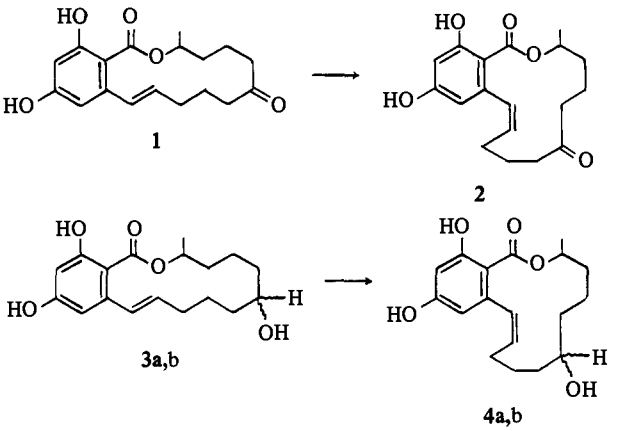


Table I. Uterotropic Activity in Mice

Test compound[a]	Daily dose, μg/g of feed	Uterine wt, mg	% body wt
Control	25	11.5	0.049
1	25	28.2	0.114
2	25	25.7	0.107
3a	50	11.2	0.050
4a	50	32.1	0.139
	100	51.8	0.226
3b	6.25	19.1	0.079
4b	3.125	32.2	0.133
	6.25	49.3	0.208

[a] In each cis-trans pair, the trans isomer tested came from the same lot as the material used in the photochemical conversion to its corresponding cis isomer.

The uterotropic activity data are summarized in Table I. In zearalenone, the cis isomer has slightly less activity than the trans isomer, but in the zearalenols, both cis isomers have substantially more activity than their respective trans isomers.

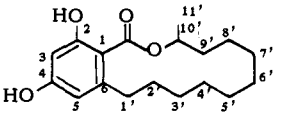
Experimental Section§

The following experimental procedure is representative for all the compounds used in this study.

cis-**Zearalenone (2).** A solution of *trans*-zearalenone (10.0 g) in 500 ml of methanol was placed in a 500-ml photochemical reactor equipped with a borosilicate glass immersion well. The system was purged overnight with nitrogen and then irradiated with a 450-W medium-pressure mercury lamp for 72–96 hr. The light yellow solution was treated with 1.0 g of KB charcoal and filtered; the methanol was removed under vacuum on a rotary evaporator to give 9.9 g of cream-colored solid. Recrystallization twice from methanol–water gave 8.8 g (88%) of *cis*-zearalenone (**2**) as white crystals, mp 134–135°. *Anal.* ($C_{18}H_{22}O_5$) C, H.

cis-**Zearalenols (4a and 4b).** The crude product obtained from

†The numbering system used throughout this paper for the zearalane system is as follows



‡For a summary of photochemical stereoisomerization of compounds containing isolated C=C, see ref 3.

§Melting points are uncorrected. Elemental analyses were performed in our laboratories. Spectra were recorded on the following instruments: uv, Bausch & Lomb Spectronic 505; ir, Perkin-Elmer Model 21 spectrophotometer; nmr, Varian Associates A-60A spectrometer (Me_2CO-d_6 as the solvent and TMS as the internal standard). All ir, uv, and nmr spectra are consistent with the assigned structures. Analyses are indicated only by symbols of the elements and the analytical results obtained for those elements were within ±0.4% of the theoretical values.