cell volume 1247.96 (32) Å^3 d_{measd} = 1.417 g/cm^3; d_{calcd} = 1.420 g/cm^3; Z = 4. For racemic **20a**, the corresponding data were as follows: monoclinic, space group $P2_1/c$; a = 12.886 (2) Å; b = 8.179 (1) Å; c = 17.042 (2) Å; β = 109.63 (1)°; cell volume 1691.77 (34) Å^3; d_{measd} = 1.315 g/cm^3; d_{calcd} = 1.313 g/cm^3; Z = 4.

Intensity data were collected on a Rigaku automated four-circle diffractometer in ω-2θ scan mode within the range $3 \leq 2\theta \leq 50°$ with Mo Kα radiation (λ = 0.71069 Å). Crystals were 0.4 × 0.2 × 0.4 mm in size for *cis*-**18a**·HCl and 0.3 × 0.2 × 0.5 mm in size for **20a**. Independent reflections, 2195, are obtained for *cis*-**18a**·HCl and for **20a**, 2974, of which weak 320 and 302 reflections were considered to be zero (under background in their counts). The data were corrected for Lorentz and polarization factors. The variance for each reflection was estimated by the equation $\sigma^2(|F_o|) = \sigma_p^2 + qF_o$, where σ_p is from counting statistics and q was derived from the variation among the monitered reflections;[23] $q = 4.5 \times 10^{-6}$ for *cis*-**18a**·HCl and 1.8×10^{-6} for **20a**.

The structures were solved by the direct method using the MULTAN program,[24] and their parameters were refined by the block-diagonal matrix least-squares method including all the hydrogen atoms. The quantity minimized was $\sum\omega(|F_o| - |F_c|)^2$, where $\omega = 1/\sigma^2(|F_o|)$. In least-squares calculations, zero reflections, except those for which $|F_c| < F_{lim}$, were included by assuming $F_o = F_{lim}$ and $\omega = \omega(F_{lim})$, where F_{lim}, an observational threshhold value, was 1.99 for *cis*-**18a**·HCl and 1.24 for **20a**. The refinement was terminated when the maximum shift of parameters of non-hydrogen atoms were 0.10σ for *cis*-**18a**·HCl and 0.67σ for **20a**. The final R values were 0.045 (0.039 for $F_o > 3/\omega$) and 0.051 (0.048), respectively. Atomic scattering factors used were taken from International Tables for X-ray Crystallography (1974).[25] Final atomic coordinates, thermal parameters, and bond lengths and angels are listed in Tables VIa-c and VIIa-c.[26]

Biological Studies. Eight to ten-week old male mice of the ICR or CDF_1 (Balb/c × DBA/2Cr) strain, purchased from Charles-River Japan, Inc., were used. Administration of the compounds to mice was performed in a saline solution for **17a**, **18a**, and levamisole and in a suspension in saline containing 1% Me_2SO for the other hexahydronaphthimidazothiazoles and **21**.

Plaque-Forming Cell (PFC) Assay. Groups of four mice were immunized intravenously with sheep red blood cells (SRBC) (1×10^8) suspended in phosphate-buffered saline (PBS; 0.1 mL). After 24 h, the test compounds were administered subcutaneously in the inguinal region. Four days after the administration, the mice were sacrificed, and hemolytic plaque-forming cells in the spleen were enumerated according to the method of Cunningham.[17]

Delayed-Type Hypersensitivity Reaction (DHR). Groups of four mice were sensitized by injection of a suspension of SRBC (1×10^8) in PBS (0.05 mL) into the footpad of one hind leg, and the test compounds were administered subcutaneously in the inguinal region. Four days later, a suspension of SRBC (1×10^8) in PBS (0.05 mL) was injected into the footpad of the other hind leg. Thickness of the hind feet was measured with a dial thickness gauge (Peacock Model G, Ikeda Rika Ltd., Tokyo) just before and 24 h after the second injection of SRBC. Increase in foot thickness was calculated in the following way: increase in foot thickness = foot thickness 24 h after injection of SRBC minus foot thickness just before injection of SRBC.

Acute Toxicity LD_{50}. The test compounds were administered intravenously or subcutaneously to groups of six mice, and the mice were observed for a period of 2 weeks. The compounds were examined at three to five dose levels selected from 400, 300, 150, 80, 40, 20, and 10 mg/kg. The LD_{50} value of each compound was calculated by the method of Litchfield-Wilcoxon.[27]

Acknowledgment. The authors thank M. Asano and S. Kimura for mass spectral measurement. Particular appreciation is expressed to S. Ishimoto and Dr. A. Mifune for their support of this investigation.

Supplementary Material Available: Physical and spectral data for compounds **6**, **8**, **9**, **11**, **12**, and **15** (Table V) and fractional coordinates, thermal parameters, bond lengths, and bond angles for *cis*-**18a**·HCl (Table VIa-c) and **20a** (Table VIIa-c) (12 pages). Ordering information is given on any current masthead page.

(23) L. E. McCandish and G. H. Staut, *Acta Crystallogr., Sect. A*, **31**, 245 (1975).
(24) G. Germain, P. Maine, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).
(25) "International Tables for X-ray Crystallography", Vol. IV, J. A. Ibers and W. C. Hamilton, Eds., Kynoch Press, Birmingham, England, pp 71-147.
(26) Tables VIa-c and VIIa-c are included in the microfilm edition of this journal.
(27) J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).
(28) D. Thienpont, D. F. J. Vanparijs, A. H. M. Raeymaekers, J. Vanderberk, P. J. A. Demoen, F. T. Tn. Allewijn, R. P. H. Marsboon, C. J. E. Niemegeers K. H. L. Schellekens, and P. A. J. Janssen, *Nature (London)*, **209**, 1084 (1966).

Synthesis and Antiallergic Properties of Some 4*H*,5*H*-Pyrano[3,2-*c*][1]benzopyran-4-one, 4*H*,5*H*-[1]Benzothiopyrano[4,3-*b*]pyran-4-one, and 1,4-Dihydro-5*H*-[1]benzothiopyrano[4,3-*b*]pyridin-4-one Derivatives

Adolf Philipp, Ivo Jirkovsky,*

Chemistry Department

and René R. Martel

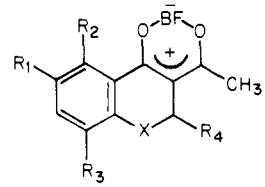
Pharmacology Department, Ayerst Laboratories, Montréal, Québec, Canada, H3C 3J1. *Received April 3, 1980*

A series of novel 2-carboxylic acids of the title ring systems has been synthesized from the corresponding 3-acetyl-4*H*-[1]benzopyran-4-one and benzothiopyran-4-one. These acids were examined for their ability to inhibit the rat passive cutaneous anaphylaxis; the pyridinone carboxylic acids **6** displayed a higher degree of iv and ip anaphylactic activities than their pyranone analogues **5**. The potassium salt **5a** (R_6 = K) was the only compound that exhibited a moderate oral activity.

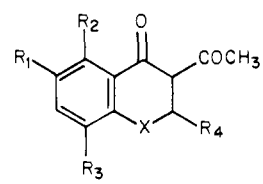
The cromoglycate molecule[1,2] has become a prototype that has led to the preparation of numerous compounds embodying the chromone moiety, and pharmacological evaluation of the first generation of these analogues has

0022-2623/80/1823-1372$01.00/0

Table I[a]



2c-i



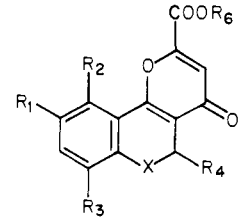
3a-i

compd no.	ref[b]	formula[c]	mp, °C	rx solvent[d]	% yield
2c	23	$C_{11}H_8BClF_2O_2S$	240-242	C	57
2d	23, 24	$C_{12}H_{11}BF_2O_2S$	243-247	B	71
2e	25	$C_{12}H_{10}BClF_2O_2S$	232-233	C	95
2f	26	$C_{15}H_{17}BF_2O_2S$	107-109	C-H	50
2g	26	$C_{15}H_{17}BF_2O_2S$	106-109	C-H	68
2h	27	$C_{12}H_{11}BF_2O_2S$	132-135	C	36
2i	27	$C_{11}H_9BF_2O_4S$	185-187	A-E	87
3a		$C_{11}H_{10}O_3$	73-74	B-H	44
3b		$C_{11}H_{10}O_2S$	86-87	E	86
3c		$C_{11}H_9ClO_2S$	96-98	B-H	82
3d		$C_{12}H_{12}O_2S$	39-42	B-H	60
3e		$C_{12}H_{11}ClO_2S$	82-85	B-H	68
3f		$C_{15}H_{18}O_2S$	oil[e]		54
3g		$C_{15}H_{18}O_2S$	oil[e]		56
3h		$C_{12}H_{12}O_2S$	81-83	B-H	92
3i		$C_{11}H_{10}O_4S$	155-156	B	85

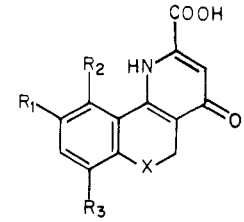
[a] See Scheme I for X and R_{1-4} designation. [b] Reference for the starting material. [c] All crystalline compounds analyzed correctly for C and H (and N where present) within ±0.4% of theoretical values. [d] A = acetone, B = benzene, C = chloroform, D = dimethyl sulfoxide, E = ether, H = hexane, M = methanol, T = acetonitrile, W = water. [e] Oily compounds exhibiting IR, NMR, and mass spectra consistent with the assigned structure.

revealed that the antianaphylactic activity is largely confined to derivatives of 4-oxo-4*H*-[1]benzopyran-2-carboxylic acids.[3-5] Also, it was established that the 5-tetrazolyl group might serve as an allosteric replacement for the carboxyl.[3] Further generalizations regarding structural requirements for the antianaphylactic activity follow from the studies of heterocyclic carboxylic acids possessing either a fused γ-pyrone[6-10] or a fused γ-pyridinone ring.[11-15] With 1,4-dihydro-4-oxoquinaldic acid[11,14]

Table II[a,b]



5a-i



6b-g,j

no.	R_6	formula[c]	mp, °C	rx solvent[d]	% yield
5a	Me	$C_{14}H_{10}O_5$	173-174	C-E	45
5a	K	$C_{13}H_7KO_5$	>300	M	98
5a		$C_{13}H_8O_5$	253-254	M	84
5b		$C_{13}H_8O_4S$	251-253	C	53
5b[e]		$C_{15}H_{15}NO_5S$	170-172	M-T	88
5c	Me	$C_{14}H_9ClO_4S$	220-222	C-E	52
5c		$C_{13}H_7ClO_4S$	283	D-W	88
5c[e]		$C_{15}H_{14}ClNO_5S$	215-217	M-E	53
5d	Me	$C_{15}H_{12}O_4S$	167-168	M	78
5d		$C_{14}H_{10}O_4S$	282-283	M-E	93
5d[e]		$C_{16}H_{17}NO_5S$	217-219	M-E	94
5e	Me	$C_{15}H_{11}ClO_4S$	192-194	C-E	41
5e		$C_{14}H_9ClO_4S$	264-267	M-W	96
5e[e]		$C_{16}H_{16}ClNO_5S$	107-110	M-E	66
5f	Me	$C_{18}H_{18}O_4S$	133-134	C-E	56
5f		$C_{17}H_{16}O_4S$	228-230	E	95
5f[e]		$C_{19}H_{23}NO_5S$	197-199	M-E	80
5g	Me	$C_{18}H_{18}O_4S$	127	E	46
5g		$C_{17}H_{16}O_4S$	261-263	C	42
5g[e]		$C_{19}H_{23}NO_5S$	205-207	M-E	69
5h	Me	$C_{15}H_{12}O_4S$	153-155	M	44
5h		$C_{14}H_{10}O_4S$	215-217	C	68
5h[e]		$C_{16}H_{17}NO_5S$	163-165	M-E	83
5i	Me	$C_{14}H_{10}O_6S$	212-214	C-E	67
5i		$C_{13}H_8O_6S$	278-279	M	98
6b		$C_{13}H_9NO_3S$	256-257	D-W	84
6b[e]		$C_{15}H_{16}N_2O_4S$	158-161	M-E	55
6c		$C_{13}H_8ClNO_3S$	282-283	D-W	94
6c[e]		$C_{15}H_{15}ClN_2O_4S$	242-243	M-E	60
6d		$C_{14}H_{11}NO_3S$	280-281	D-W	99
6d[e]		$C_{16}H_{18}N_2O_4S$	227-230	M-E	72
6e		$C_{14}H_{10}ClNO_3S$	272-273	D-W	96
6e[e]		$C_{16}H_{17}ClN_2O_4S$	202-204	M-E	85
6f		$C_{17}H_{17}NO_3S$	273-274	D-W	98
6f[e]		$C_{19}H_{24}N_2O_4S$	204-206	M-E	65
6g		$C_{17}H_{17}NO_3S$	269	D-W	99
6g[e]		$C_{19}H_{24}N_2O_4S$	228-231	M-E	91
6j		$C_{17}H_{17}NO_5S$	263-264	A-W	67

[a] See footnote *a*, Table I. [b] R_6 = H unless otherwise stated. [c,d] See corresponding footnotes to Table I. [e] 2-Hydroxyethylammonium salt.

as a starting point, several series of polynuclear oxoquinaldic acids were synthesized,[12-15] and a molecular modification of the oxoquinaldic acid provided a new class of antiallergic agents—oxanilic acids.[16-18]

The ongoing search for new, more potent, orally active congeners of cromoglycate appears to be useful to accumulate information concerning the structure–activity re-

(1) J. S. G. Cox, J. E. Beach, A. M. J. N. Blair, A. J. Clarke, J. King, T. B. Lee, D. E. E. Loveday, G. F. Moss, T. S. C. Orr, J. Y. Ritchie, and P. Sheard, *Adv. Drug Res.*, **5**, 115 (1970).

(2) H. Cairns, C. Fitzmaurice, D. Hunter, P. B. Johnson, J. King, T. B. Lee, G. H. Lord, R. Minshull, and J. S. G. Cox, *J. Med. Chem.*, **15**, 583 (1972).

(3) G. P. Ellis and D. Shaw, *J. Med. Chem.*, **15**, 865 (1972).

(4) G. P. Ellis and G. Barker, *Progr. Med. Chem.*, **9**, 66–116 (1972).

(5) G. Barker, G. P. Ellis, and D. Shaw, *J. Med. Chem.*, **16**, 87 (1973).

(6) J. B. Wright and H. G. Johnson, *J. Med. Chem.*, **16**, 861 (1973).

(7) A. Nohara, H. Kuriki, T. Saijo, K. Ukawa, T. Murata, M. Kanno, and Y. Sanno, *J. Med. Chem.*, **18**, 34 (1975).

(8) J. R. Bantick, H. Cairns, A. Chambers, R. Hazard, J. King, T. B. Lee, and R. Minshull, *J. Med. Chem.*, **19**, 817 (1976).

(9) J. P. Devlin, K. Freter, and P. B. Stewart, *J. Med. Chem.*, **20**, 205 (1977).

(10) J. P. Devlin, A. Bauen, G. J. Possanza, and P. B. Stewart, *J. Med. Chem.*, **21**, 480 (1978).

(11) C. M. Hall, H. G. Johnson, and J. B. Wright, *J. Med. Chem.*, **17**, 685 (1974).

(12) D. P. Evans, D. J. Gilman, D. S. Thomson, and W. S. Waring, *Nature (London)*, **250**, 592 (1974).

(13) C. M. Hall, J. B. Wright, H. G. Johnson, and A. J. Taylor, *J. Med. Chem.*, **20**, 1337 (1977).

(14) E. H. Erickson, L. R. Lappi, T. K. Rice, K. F. Swingle, and M. Van Winkle, *J. Med. Chem.*, **21**, 984 (1978).

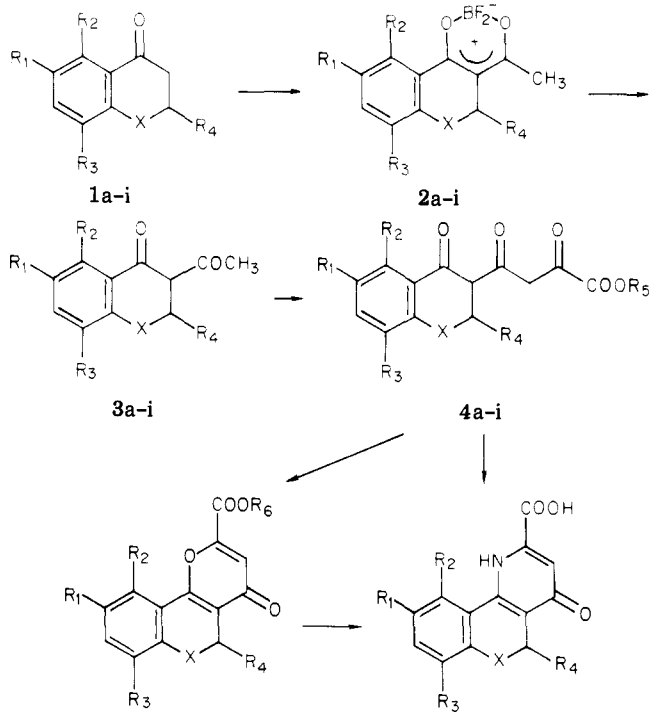
(15) J. J. Wade, E. H. Erickson, R. F. Hegel, L. R. Lappi, and T. K. Rice, *J. Med. Chem.*, **21**, 941 (1978).

(16) J. H. Sellstedt, C. J. Guinosso, A. J. Begany, S. C. Bell, and M. Rosenthale, *J. Med. Chem.*, **18**, 926 (1975).

(17) J. B. Wright and H. G. Johnson, *J. Med. Chem.*, **20**, 166 (1977).

(18) J. B. Wright, C. M. Hall, and H. G. Johnson, *J. Med. Chem.*, **21**, 930 (1978).

Scheme I



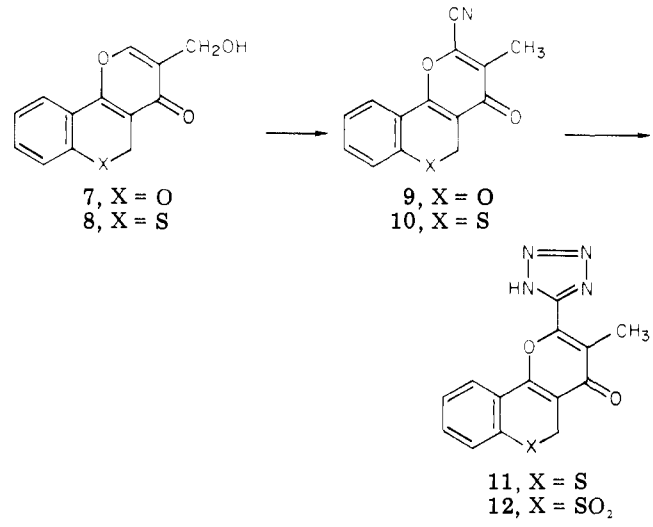
	X	R_1	R_2	R_3	R_4
a	O	H	H	H	H
b	S	H	H	H	H
c	S	Cl	H	H	H
d	S	CH_3	H	H	H
e	S	H	Cl	CH_3	H
f	S	*n*-Bu	H	H	H
g	S	*s*-Bu	H	H	H
h	S	H	H	H	CH_3
i	SO_2	H	H	H	H
j	SO_2	*s*-Bu	H	H	H

lationships and establish some criteria for a meaningful design of these compounds. In this report we describe the syntheses and antianaphylactic activities of a series of 4-oxo-4*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-,[19] 4-oxo-4*H*,5*H*-[1]benzothiopyrano[4,3-*b*]pyran-, and 1,4-dihydro-4-oxo-5*H*-[1]benzothiopyrano[4,3-*b*]pyridine-2-carboxylic acids.

Chemistry. Most synthetic studies dealing with the preparation of compounds structurally related to cromoglycate have employed the classical Kostanecki reaction,[20,21] which involves condensation of aromatic *o*-hydroxy ketones with dialkyl oxalates. As described below, we have now extended the applicability of this reaction to enolizable diketones, **3** (X = O or S), and synthesized a series of tricyclic esters and carboxylic acids, **5**. The general synthetic route is outlined in Scheme I and novel compounds are listed in Tables I and II.

Recently, we have described[22] the preparation of the

Scheme II



7, X = O
8, X = S

9, X = O
10, X = S

11, X = S
12, X = SO_2

dioxaborins **2a,b** by the reaction of chroman-4-one (**1a**) and thiochroman-4-one (**1b**) with a boron trifluoride–acetic anhydride–acetic acid mixture. Treatment of **2a** with sodium acetate under mild conditions afforded the free diketone **3a**. Condensation of this compound with diethyl oxalate was carried out in dimethylformamide in the presence of an excess of sodium hydride. By changing the workup procedure we were able to isolate either the triketo ester **4a** (R_5 = Et) or the corresponding carboxylic acid **4a** (R_5 = H). Both compounds gave the tricyclic methyl ester **5a** (R_6 = Me) upon treatment with hot methanolic hydrogen chloride, and subsequent hydrolysis with aqueous potassium hydroxide yielded the crystalline salt **5a** (R_6 = K), which was converted to 4-oxo-4*H*,5*H*-pyrano[3,2-*c*]-[1]benzopyran-2-carboxylic acid (**5a**; R_6 = H).

In contrast to 3-acetylchroman-4-one (**3a**), the thio analogues **3b–i** were more stable and, thus, their condensations with diethyl oxalate resulted in high yields of mixtures of **5b–i** (R_6 = H) and their open-chain procursors **4b–i** (R_5 = H). The ratio of these products was estimated on the basis of their NMR spectra, comparing the integrated intensity of the aromatic region with that of a single resonance at δ 6.9–7.1 (=CHCO) which was indicative of the tricyclic structure **5**. To complete formation of the pyrone ring, the latter mixtures were heated with hydrochloric acid in acetic acid; however, treatment of the mixtures **4** + **5** (R_5 = R_6 = H) with hot methanolic hydrogen chloride, purification of the resultant methyl esters **5** (R_6 = Me), and their saponification to the corresponding carboxylic acids **5** (R_6 = H) appeared to be more convenient. Both **4** and **5** (X = S; R_5 = R_6 = H) or their mixtures produced the pyridinone carboxylic acids **6** upon boiling with ammonium hydroxide.

The sulfones **5i** (R_6 = Me or H) were synthesized from thiochroman-4-one 1,1-dioxide (**3i**) according to Scheme I or, alternatively, by *m*-chloroperbenzoic acid oxidation of **5b** (R_6 = Me or H, respectively). The sulfone **6j** was prepared by reaction of the carboxylic acid **6g** with hy-

(19) While our work was in progress, the construction of 2-methyl-4*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-4-ones from 3-acetylchroman-4-ones was described in the form of a preliminary communication and exemplified by the synthesis of di-*O*-methylcitromycin which is a degradation product of the fungal metabolite citromycetin; cf. F. M. Dean, S. Murray, and W. Taylor, *J. Chem. Soc., Chem. Commun.*, 440 (1974).

(20) S. von Kostanecki, L. Paul, and J. Tambor, *Chem. Ber.*, **34**, 2475 (1901).

(21) R. Heywang and S. von Kostanecki, *Chem. Ber.*, **35**, 2887 (1902).

(22) A. Philipp and I. Jirkovsky, *Can. J. Chem.*, **57**, 3292 (1979).

(23) I. Degani, R. Fochi, and G. Spunta, *Boll. Sci. Fac. Chim. Ind. Bologna*, **24**, 75–91 (1966); *Chem. Abstr.*, **66**, 46292*n*.

(24) F. Krollpfeiffer and H. Schultze, *Chem. Ber.*, **56**, 1819 (1923).

(25) F. Bossert and R. Goennert, *Abh. Med. Chem. Forsch. Farbwerke Hoechst A.G.*, **7**, 367 (1963); *Chem. Abstr.*, **60**, 3236*g*.

(26) A. M. Kuliev, A. B. Kuliev, and F. N. Mamedov, *Zh. Obshch. Khim.*, **34**, 993 (1964).

(27) F. Arndt, *Chem. Ber.*, **58**, 1612 (1925).

Table III. Antianaphylactic Activity

compd[a]	PCA ID_{50}, mg/kg iv[b]	PCA ID_{50}, mg/kg ip[b]
DSCG[c]	1 (0.6-1.4)	16.6 (15.0-18.0)
5a	12	nt[d]
5b	25	>100
5c	28	>100
5d	19	>30
5e	30	>100
5f	19	>30
5g	25	>30
5h	8.4 (7.0-10.0)	29
5i	>30	>100
6b	5.3 (4.5-6.5)	>30
6c	3.3 (2.8-4.0)	33
6d	6.9 (5.8-8.1)	34
6e	>30	>30
6f	12 (10.5-14.0)	20
6g	8.2 (6.9-10.0)	27
6j	>30	>30
7	nt[d]	23
8	>30	>30
11	nt[d]	>30
12	nt[d]	100

[a] The carboxylic acid 5a was tested as the potassium salt; carboxylic acids 5b-6g were evaluated in the form of 2-hydroxyethylammonium salts. The corresponding esters were consistently less active, and as our study progressed we decided to characterize them as chemical intermediates only. [b] Numbers in parentheses are 95% confidence limits. [c] Disodium cromoglycate. [d] Not tested.

drogen peroxide in formic acid.

In view of the possible enhancement of antianaphylactic effects obtained on replacement of the carboxyl by the 5-tetrazolyl group,[3,28] we were interested in the requisite carbonitriles derived from carboxylic acids **5** (R_6 = H). Unfortunately, a convenient method for the preparation of these nitriles could not be established. In connection with other studies in the series of 4*H*,5*H*-pyran[3,2-*c*]-[1]benzopyran-4-ones and 4*H*,5*H*-[1]benzothiopyrano-[4,3-*b*]pyran-4-ones, we have found[22] that 3-methyl-2-carbonitriles **9** and **10** are readily accessible form 3-hydroxymethyl derivatives **7** and **8** (Scheme II), whose mesylates react with sodium cyanide in aqueous tetrahydrofuran to afford the desired nitriles **9** and **10**. Heating of the nitrile **10** with sodium azide and ammonium chloride in dimethylformamide resulted in the formation of **11**, which was oxidized with *m*-chlorperbenzoic acid to furnish the sulfone **12**.

Biological Results. Compounds were examined for their ability to inhibit the passive cutaneous anaphylaxis (PCA) in rats as described under Experimental Section. The dose of compound required to inhibit the response by 50% (ID_{50}) was determined and the test results are listed in Table III. In the present series, there seems to be little correlation between iv and ip activities. The pyridinone carboxylic acids **6** displayed a higher degree of antianaphylactic activity than the analogous acids **5**. Of the latter series, the 5-methyl derivative **5h** (R_6 = H) was the most potent compound; unfortunately, the corresponding pyridinone carboxylic acid **6h** was found to be unstable and could not be evaluated. The introduction of large lipophilic groups, such as *n*-butyl and *sec*-butyl (acids **6f** and **6g**) resulted in an enhancement of the ip activity. The 10-chloro-7-methyl derivatives **5e** (R_6 = H) and **6e**, the sulfones **5i** (R_6 = H) and **6j**, and the tetrazoles **11** and **12** were essentially inactive. The potassium salt **5a** (R_6 = K) was the only compound that exhibited a moderate oral activity at 10 mg/kg.

(28) A. Nohara, H. Kuriki, T. Saijo, H. Sugihara, M. Kanno, and Y. Sanno, *J. Med. Chem.*, **20**, 141 (1977).

Experimental Section

Melting points are uncorrected. Infrared specta were determined on a Perkin-Elmer 225 spectrophotometer. ^1H NMR spectra were recorded on a Varian CFT-20 instrument using tetramethylsilane as an internal standard. Only significant spectral data are reported. Column chromatographic separations were carried out on silica gel 60 (Merck, mesh 70–230) using 40 g of absorbant per gram of substance.

Dioxaborins 2c–i. These compounds were prepared according to the procedure for the synthesis of dioxaborins **2a,b**.[22] **Diketones 3.** Compounds **3a–i** (Table I) were prepared from the appropriate dioxaborins **2a–i**; the following example illustrates the general procedure.

3-Acetyl-6-chloro-4*H*-[1]benzothiopyran-4-one (3c). A mixture of **2c** (46.7 g, 0.162 mol), glacial AcOH (275 mL), and AcONa (184 g, 2.25 mol) was heated on a steam bath for 1 h. The resultant solution was poured on ice and extracted with Et_2O, and the extract was washed with a solution of $NaHCO_3$ and brine. The Et_2O phase was evaporated and the residue was chromatographed on a short column of silica gel with benzene–hexane (1:1) to afford 31.9 g (82%) of **3c**, yellow crystals, mp 96–98 °C.

Compounds **3f** and **3g** were isolated at oils. **3f**: IR ($CHCl_3$) 1605, 1580 cm^{-1}; NMR ($CDCl_3$) δ 0.91 (t, J = 7 Hz, 3 H, CH_3), 1.5 (m, 4 H, CH_2), 2.27 (s, 3 H, $COCH_3$), 2.63 (t, J = 7 Hz, 2 H, benzylic CH_2), 3.7 (s, 2 H, CH_2S), 7.19 (singlet with fine splitting, 2 H, H-7 and H-8), 7.83 (singlet with fine splitting, 1 H, H-5), 16.55 (s, 1 H, enolic OH); MS *m/e* 262 (M^+). **3g**: IR ($CHCl_3$) 1600, 1580 cm^{-1}; NMR ($CDCl_3$) δ 0.83 (t, J = 7 Hz, 3 H, CH_3), 1.25 (d, J = 7 Hz, 3 H, CH_3), 1.53 (m, 2 H, CH_2), 2.26 (s, 3 H, $COCH_3$), 2.60 (m, 1 H, benzylic CH), 3.70 (s, 2 H, CH_2S), 7.22 (singlet with fine splitting, 2 H, H-7 and H-8), 7.83 (singlet with fine splitting, 1 H, H-5), 16.65 (s, 1 H, enolic OH); MS *m/e* 262 (M^+).

The diketosulfone **3i** precipitated when poured on ice and was isolated by filtration.

4-(4-Oxo-4*H*-[1]benzopyran-3-yl)-2,4-dioxobutanoic Acid and Its Ethyl Ester (4a, R_5 = H, Et). A solution of **3a** (1.8 g, 9.5 mmol) in anhydrous THF (20 mL) was added dropwise to a stirred suspension of NaH (57% oil suspension, 1.17 g, 29 mmol) in THF (30 mL) and the mixture was refluxed under N_2 for 15 min. A solution of diethyl oxalate (1.39 g, 9.5 mmol) in THF (20 mL) was added dropwise at 60 °C and a gentle reflux was continued for 15 h.

Isolation of the Acid. A part of the reaction mixture was evaporated to dryness, and the residues was dissolved in ice-cold H_2O and washed with Et_2O. The aqueous phase was acidified with 6 N HCl and extracted with $CHCl_3$. Solvent removal in vacuo, followed by crystallization from MeOH–$CHCl_3$, gave the title acid (30% yield): mp 170 °C (resolidified, mp 247–249 °C); IR (Nujol) broad carboxylic OH, 1710, 1610 cm^{-1}.

Isolation of the Ethyl Ester. The reaction mixture was cooled to −40 °C and neutralized with 50% aqueous AcOH, and the volatiles were removed in good vacuo. The residue was partitioned between H_2O and $CHCl_3$, the organic layer was evaporated, and the product was purified by column chromatography (silica–$CHCl_3$). The title ethyl ester was obtained in a 28% yield: mp 117–119 °C (Et_2O); IR ($CHCl_3$) 1735, 1610 cm^{-1}.

4-Oxo-4*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-2-carboxylic Acid and Its Methyl Ester (5a, R_6 = Me, H). A solution of **4a** (R_5 = Et) in MeOH was saturated with HCl, refluxed overnight, and stripped with a rotavapor. The residue was chromatographed on silica gel. The benzene–ethyl acetate (4:1) eluate gave the methyl ester **5a** (R_6 = Me), which was recrystallized from $CHCl_3$–Et_2O: mp 173–174 °C; yield 45%.

This ester was dissolved in 1.5% methanolic KOH, and the solution was stirred at room temperature overnight and concentrated in vacuo. The crystalline precipitate **5a** (R_6 = K) was dissolved in H_2O and acidified with diluted HCl to give **5a** (R_6 = H): mp 253–254 °C: yield 84%.

General Synthesis of Methyl Esters 5b–i. 9-Butyl-4-oxo-4*H*,5*H*-[1]benzothiopyrano[4,3-*b*]pyran-2-carboxylic Acid Methyl Ester (5f). A solution of **3f** (10.65 g, 40.6 mmol)

in anhydrous THF (50 mL) was added dropwise to a stirred suspension of NaH (57% oil suspension, 5.13 g, 127 mmol) in THF (25 mL), and the mixture was heated under N_2 at 60 °C for 1 h, the reaction mixture was maintained at 60 °C overnight, and then evaporated under reduced pressure. The residue was dissolved in H_2O, and this solution was warmed to 40 °C, kept at ambient temperature for several hours, and washed with Et_2O. The aqueous phase was layered over hot $CHCl_3$, acidified with concentrated HCl, and stirred vigorously for 1 h. The $CHCl_3$ phase was separated and stripped on a rotavapor to give a 6:4 mixture (10 g) of **4f** (R_5 = H) and **5f** (R_6 = H), respectively: NMR (Me_2SO-d_6) δ 7.01 (s, 0.4 H, =CH).

This mixture was dissolved in MeOH (750 mL), saturated with dry HCl, refluxed overnight, and evaporated in vacuo. The residue was chromatographed on a column of silica gel packed in $CHCl_3$ to afford 7.5 g (56%) of **5f**: mp 133–134 °C ($CHCl_3$–Et_2O).

4-Oxo-4*H*,5*H*-[1]benzothiopyrano[4,3-*b*]pyran-2-carboxylic Acid Methyl Ester 6,6-Dioxide (5i). A solution of *m*-chloroperbenzoic acid (2.07 g, 12 mmol) in $CHCl_3$ (50 mL) was added dropwise to a stirred solution of **5b** (R_6 = Me; 1.37 g, 5 mmol) in $CHCl_3$ (50 mL) at 5 °C. The stirring was continued at room temperature for 4 h, and the reaction mixture was washed with aqueous $NaHCO_3$ and H_2O, dried, and evaporated to dryness. The residue was crystallized from $CHCl_3$–Et_2O: mp 212–214 °C; yield 1.03 g (67%).

General Synthesis of Carboxylic Acids 5b–i. The aforementioned procedure for the hydrolysis of **5a** (R_6 = Me) to the corresponding carboxylic acid **5a** (R_6 = H) was adopted for the preparation of **5b–i** from their methyl esters.

2-Hydroxyethylammonium salts of **5b–h** were obtained by adding methanolic 2-aminoethanol to a solution (or suspension) of the corresponding acid in MeOH.

General Synthesis of Carboxylic Acids 6b–g. 1,4-Dihydro-4-oxo-5*H*-[1]benzothiopyrano[4,3-*b*]pyridine-2-carboxylic Acid (6b). A solution of **5b** (R_6 = H; 3 g, 11.5 mmol) in concentrated ammonium hydroxide (50 mL) was heated on a steam bath for 2 h and evaporated in vacuo. The residue was dissolved in H_2O (75 mL) and added to a mixture of concentrated HCl (5 mL) and ice. The precipitate was collected by filtration and washed successively with 0.07 N HCl, acetone, and Et_2O to give 2.52 g (84%) of the title acid, mp 256–257 °C (Me_2SO–H_2O).

This acid was dissolved in a methanolic solution of 2-aminoethanol (0.6 g), the resulting solution was treated with charcoal and filtered, and the filtrate was evaporated. Crystallization of the residue from MeOH–Et_2O afforded the hydroxyethylammonium salt of **6b**, mp 158–161 °C.

1,4-Dihydro-9-(1-methylpropyl)-4-oxo-5*H*-[1]benzothiopyrano[4,3-*b*]pyridine-2-carboxylic Acid 6,6-Dioxide (6j). To a suspension of **6g** (1.33 g, 4.2 mmol) in 98% HCOOH (20 mL) was added 30% H_2O_2 (3.5 mL). The resulting solution (obtained within 10 min) was stirred at room temperature for 22 h and diluted with H_2O, and the precipitate was collected by filtration. Recrystallization from aqueous acetone afforded 0.98 g (67%) of **6j**, mp 263–264 °C.

3-Methyl-4-oxo-2-(1*H*-tetrazol-5-yl)-4*H*,5*H*-[1]benzothiopyrano[4,3-*b*]pyran (11). A solution of the nitrile **10**[22] (3.14 g, 12.3 mmol), NaN_3 (0.88 g, 12.3 mmol), and NH_4Cl (0.13 g, 2.4 mmol) in DMF (18 mL) was heated at 110 °C for 18 h and evaporated in vacuo. The residue was dissolved in H_2O (50 mL), washed with ethyl acetate, and acidified with 10% HCl. The precipitate was collected by filtration and recrystallized from aqueous acetone to give 2.5 g (62%) of **11**: mp 247–248 °C; NMR (Me_2SO-d_6) δ 2.31 (s, 3 H, CH_3), 3.88 (s, 2 H, CH_2), 7.25 (m, 3 H, H-7, H-8, H-9), 7.95 (m, 1 H, H-10), 11.1 (br, 1 H, NH). Anal. ($C_{14}H_{10}N_4O_2S$) C, H, N.

3-Methyl-4-oxo-2-(1*H*-tetrazol-5-yl)-4*H*,5*H*-[1]benzothiopyrano[4,3-*b*]pyran 6,6-Dioxide (12). Compound **11** (1.75 g, 5.9 mmol) was suspended in a solution of *m*-chloroperbenzoic acid (4 g, 23 mmol) in $CHCl_3$ (200 mL) and the mixture was stirred at ambient temperature for 22 h. The solids were collected by filtration and recrystallized from MeOH to give 1.54 g (80%) of **12**: mp 268–270 °C; NMR (Me_2SO-d_6) δ 2.40 (s, 3 H, CH_3), 4.72 (s, 2 H, CH_2), 8.03 (m, 3 H, H-7, H-8, H-9), 8.46 (m, 1 H, H-10), 10.96 (br, 1 H, NH). Anal. ($C_{14}H_{10}H_4O_4S$) C, H, N.

Passive Cutaneous Anaphylaxis (PCA) Test. Adult male Charles River rats (140–160 g, six rats per group) were sensitized at two sites with an intradermal injection (0.1 mL) of rat serum containing reaginic antibodies to chicken ovalbumin. After a 48-h latent period, the animals were challenged iv with 10 mg/kg of chicken ovalbumin dissolved in a 1% solution of Evans blue. Thirty minutes later, the rats were sacrificed and skinned. The area of the dermal bluing which occurred at the sites of sensitization was measured (ca 20-mm diameter spot in the control rats) and the results were used for calculation of the drug-induced percent inhibition of this effect. For iv administration, the test compounds (30, 10, and 3 mg/kg) were injected at the same time as the antigen challenge. When given ip and po, the compounds were administered 15 min prior to the challenge. The dose that inhibited the PCA by 50% (ID_{50}) was determined graphically from a dose–response curve for each compound. Disodium cromoglycate was tested at 9, 3, 1, and 0.3 mg/kg iv and at 60, 30, 15, 8, and 4 mg/kg ip.

Studies on Anticoccidial Agents. 13. Synthesis and Anticoccidial Activity of Nitropyridine-2- and -3-sulfonamides and Derivatives

Yasuhiro Morisawa,* Mitsuru Kataoka, Hitoshi Nagahori, Toshiaki Sakamoto, Noritoshi Kitano, Kenichi Kusano, and Kiyoshi Sato

Central Research Laboratories, Sankyo Company, Ltd., Shinagawa-ku, Tokyo, Japan. *Received June 17, 1980*

Eight nitropyridinesulfonamides and pyridinesulfonamide *N*-oxides as their bioisosteres were prepared and evaluated for anticoccidial activity. Of these compounds, 2-, 4- and 5-nitropyridine-3-sulfonamides and pyridine-2- and -3-sulfonamide *N*-oxides were found to be active against *Eimeria tenella*. Thus, the relative positions, ortho or meta, of the substituents in nitropyridine-3-sulfonamides and pyridinesulfonamide *N*-oxides are important for anticoccidial activity. N-Substituted analogues of 5-nitropyridine-3-sulfonamide were also prepared and optimal anticoccidial activity was attained with the sulfonamide and its lower *N*-alkyl derivatives. The mode of action of 5-nitropyridine-3-sulfonamide was examined and found to be active in the sporozoite and the first schizogony stages.

In previous papers[1] we reported that some nitropyridinecarboxamides showed anticoccidial activity against *Eimeria tenella*. As a continuation of the study to evaluate various nitropyridine analogues, we have now synthesized

0022-2623/80/1823-1376$01.00/0