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Synthesis of (3-Carboxy-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridin-2-yl)acetic Acid Derivatives, Potential Antiarthritic Agents

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(3-Carboxy-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridin-2-yl)acetic acid derivatives (**3** and **4**) were found to possess potent antiarthritic activity in the rat adjuvant arthritis model. The mode of action of these compounds differs from that of acidic antiinflammatory drugs. Various modifications in these compounds (*e.g.*, elongation, removal, or substitution of the methylene group of the acetic acid moiety; and substitution of the benzene ring) were made in order to study the structure–activity relationships. However, it was found that the structural requirements for the compounds to show activity are rather severe.

Keywords——5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine; acetic acid; propionic acid; 4-oxo-4*H*-1-benzopyran; adjuvant arthritis; structure–activity relationships; acetonedicarboxylate; dicarboxylic acid

Non-steroidal antiinflammatory drugs (NSAIDs) are frequently used to relieve joint pain and swelling in patients with rheumatoid arthritis. Most NSAIDs are acidic compounds, usually arylacetic acid analogues, and exert their effects by inhibiting prostaglandin synthesis. However, NSAIDs have some drawbacks: they are ineffective in retarding the progression of the disease and they have a common gastrointestinal side effect characteristic of aspirin-like compounds. Accordingly, much effort is being devoted to searching for agents defined as disease-modifying anti-rheumatic drugs (DMARDs).[1)]

For this purpose, research on compounds that show no anti-edematous activity and inhibit rat adjuvant arthritis has been carried out; Robenzarit® (CCA) (**1**)[2)] and benzoylacetonitriles[3)] could be such compounds. During our investigations on the antiallergic activity of 5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carboxylic acids,[4)] we found that disodium (3-carboxylato-7-ethyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridin-2-yl)acetate (**4a**) showed no anti-edematous activity, regardless of its structural analogy with arylacetic acids, and was effective in suppressing the development of rat adjuvant arthritis. In this paper we describe the synthesis of **4a** and related compounds, and their effect on rat adjuvant arthritis.

Chemistry

The reaction of 6-ethyl-4-oxo-4*H*-1-benzopyran-3-carbonitrile (**2a**)[5)] with dimethyl 1,3-acetonedicarboxylate in the presence of piperidine gave methyl (7-ethyl-3-methoxycarbonyl-

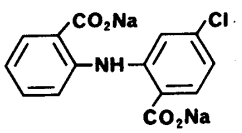

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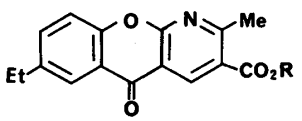
Fig. 1



5a: R=Me
5b: R=H

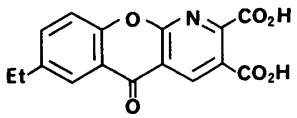


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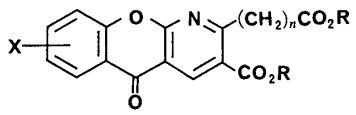
Fig. 2

TABLE I. 5-Oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridines



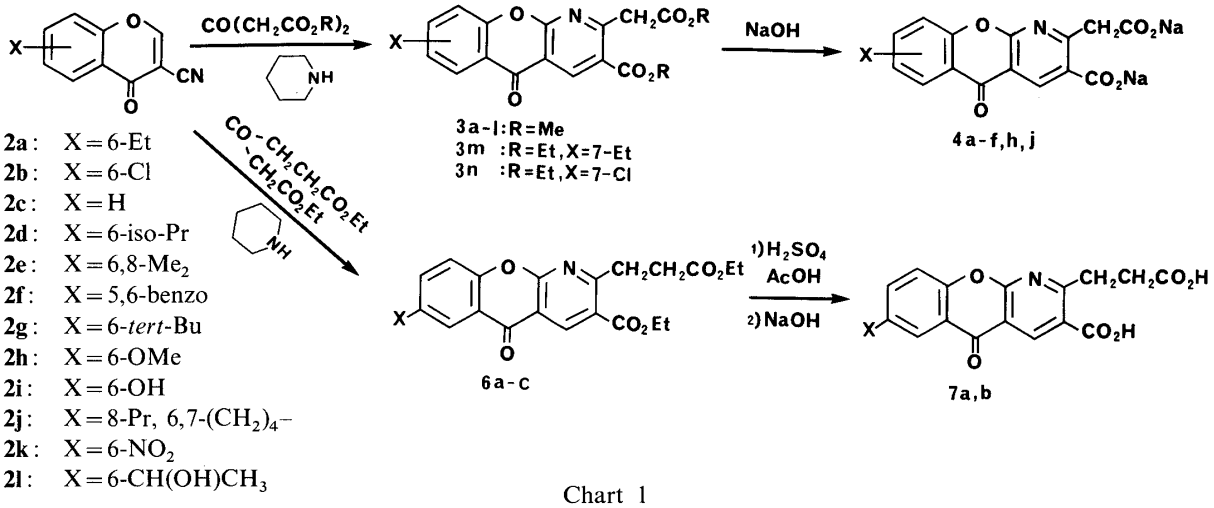
Compd.	X	R	*n*	Recryst. solvt.[a]	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
3a	7-Et	Me	1	A	29	142—143	$C_{19}H_{17}NO_6$	64.22	4.82	3.94
								(64.33	4.66	3.89)
3b	7-Cl	Me	1	B	35.7	192—193	$C_{17}H_{12}ClNO_6$	56.45	3.34	3.87
								(56.25	3.18	3.83)
3c	H	Me	1	B	49.4	168—169	$C_{17}H_{13}NO_6$	62.38	4.00	4.28
								(62.39	4.01	4.38)
3d	7-iso-Pr	Me	1	A	71	135—136	$C_{20}H_{19}NO_6$	65.03	5.19	3.79
								(65.22	4.97	3.71)
3e	7,9-Me_2	Me	1	B	57.9	197—198	$C_{19}H_{17}NO_6$	64.22	4.82	3.94
								(64.53	4.91	4.12)
3f	6,7-Benzo	Me	1	B	59.7	240—245	$C_{21}H_{15}NO_6$	66.84	4.01	3.71
								(66.43	4.03	3.65)
3g	7-*tert*-Bu	Me	1	C	60.9	152—153	$C_{21}H_{21}NO_6$	65.79	5.52	3.65
								(65.70	5.40	3.62)
3h	7-OMe	Me	1	D	60.6	175—176.5	$C_{18}H_{15}NO_7$	60.51	4.23	3.92
								(60.66	4.21	4.06)
3i	7-OH	Me	1	B	51.3	234.5—235.5	$C_{17}H_{13}NO_7$	59.48	3.82	4.08
								(59.56	3.86	4.28)
3j	9-Pr	Me	1	B	79.2	156—157	$C_{24}H_{25}NO_6$	68.07	5.95	3.31
								(68.08	5.67	3.38)
3k	7,8-$(CH_2)_4$–7-NO_2	Et	1	E	67.6	147.5—148.5	$C_{19}H_{16}N_2O_8$	57.00	4.03	7.00
								(57.15	4.16	7.13)
3l	7-MeCH(OH)–	Et	1	F	56.3	124—126	$C_{21}H_{21}NO_7$	63.15	5.30	3.51
								(63.28	5.11	3.63)
3m	7-Et	Et	1	F	35.8	123—124	$C_{21}H_{21}NO_6$	65.78	5.52	3.65
								(65.70	5.21	3.43)
3n	7-Cl	Et	1	D	64.9	148—149	$C_{19}H_{16}ClNO_6$	58.55	4.14	3.59
								(58.66	4.09	3.47)
3o	7-Ac	Et	1	E	79.0[b]	160—161	$C_{21}H_{19}NO_7$	63.47	4.82	3.53
								(63.71	4.67	3.69)
4a	7-Et	Na	1	G	80	275—280 (dec.)	$C_{17}H_{11}NNa_2O_6 \cdot 2H_2O$	50.13	3.71	3.44
								(50.14	4.20	3.46)
4b	7-Cl	Na	1	G	58.9	—[c]	$C_{15}H_6ClNNa_2O_6 \cdot 5/2\,H_2O$	42.62	2.62	3.31
								(42.57	2.26	3.30)
4c	H	Na	1	G	70.1	—[c]	$C_{15}H_7NNa_2O_6 \cdot 2H_2O$	47.50	2.92	3.69
								(47.49	2.71	3.95)
4d	7-iso-Pr	Na	1	G	71.7	—[c]	$C_{18}H_{13}NNa_2O_6 \cdot H_2O$	53.61	3.75	3.47
								(53.85	4.28	3.47)
4e	7,9-Me_2	Na	1	G	58.2	—[c]	$C_{17}H_{11}NNa_2O_6 \cdot 4/5\,H_2O$	52.94	3.29	3.63
								(52.93	3.72	3.90)
4f	6,7-Benzo	Na	1	G	57.9	—[c]	$C_{19}H_9NNa_2O_6 \cdot 6H_2O$	45.51	4.22	2.79
								(45.31	3.20	2.72)
4h	7-OMe	Na	1	J	34.8	190—200 (dec.)	$C_{16}H_9NNa_2O_7 \cdot 2H_2O$	46.96	3.20	3.42
								(47.29	3.17	3.44)
4j	9-Pr	Na	1	G	79.5	—[c]	$C_{22}H_{19}NNa_2O_6 \cdot MeOH \cdot H_2O$	56.44	5.15	2.86
	7,8-$(CH_2)_4$–							(56.77	5.38	3.03)
6a	7-Et	Et	2	F	48.6	168—170	$C_{22}H_{23}NO_6$	66.49	5.83	3.52
								(66.66	5.66	3.35)

TABLE I. (continued)

Compd.	X	R	*n*	Recryst. solvt.[a]	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
								C	H	N
6b	7-Cl	Et	2	B	40	128—129	$C_{20}H_{18}ClNO_6$	59.49	4.49	3.47
								(59.51	4.38	3.64)
6c	H	Et	2	F	21.7	150—151	$C_{20}H_{19}NO_6$	65.03	5.19	3.79
								(65.34	5.22	3.67)
7a	7-Et	H	2	H	88.7	284—287 (dec.)	$C_{18}H_{15}NO_6$	63.34	4.43	4.10
								(63.24	4.40	4.17)
7b	7-Cl	H	2	I	78.6	295—298 (dec.)	$C_{16}H_{10}ClNO_6$	55.27	2.90	4.03
								(55.27	3.00	4.06)

a) A=MeOH, B=$CHCl_3$–MeOH, C=$CHCl_3$–iso-Pr_2O, D=$CHCl_3$–EtOH, E=AcOEt, F=EtOH, G=H_2O–MeOH, H=DMF–H_2O, I=DMF, J=H_2O–EtOH. *b*) The yield from **3n**. *c*) Indefinite.

5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridin-2-yl)acetate (**3a**) together with a trace of methyl 7-ethyl-2-methyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carboxylate (**5a**). In a similar manner, dimethyl or diethyl esters (**3b**—**n**) carrying various substituents on the benzene ring were synthesized from **2** with dimethyl or diethyl 1,3-acetonedicarboxylate (Table I). The 7-acetyl derivative (**3o**) was prepared by Jones oxidation of the 7-(1-hydroxyethyl) derivative (**3l**).



2a: X=6-Et
2b: X=6-Cl
2c: X=H
2d: X=6-iso-Pr
2e: X=6,8-Me_2
2f: X=5,6-benzo
2g: X=6-*tert*-Bu
2h: X=6-OMe
2i: X=6-OH
2j: X=8-Pr, 6,7-$(CH_2)_4$–
2k: X=6-NO_2
2l: X=6-CH(OH)CH_3

Chart 1

When **3a** was heated with $NaHCO_3$ in aqueous EtOH, the decarboxylated product **5b** was formed mainly. Therefore, to avoid decarboxylation, **3a** was hydrolyzed with 1 N NaOH in tetrahydrofuran (THF) at room temperature to give the desired **4a** in good yield. In a similar manner, **4b**—**j** were synthesized (Table I).

To test the influence of chain length and the importance of the carboxylic acid group in the acetate moiety of **4** on the activity, the propionic acid derivative (**7**), dicarboxylic acid (**8**), and monocarboxylic acid (**5b**) were prepared. The ethyl propionate derivative (**6**), synthesized from **2** and diethyl β-ketoadipate,[6] was hydrolyzed stepwise by heating in H_2SO_4–AcOH and then in 1 N NaOH. The dicarboxylic acid derivative (**8**), which lacks the methylene group of the acetic acid moiety of **4**, and the decarboxylated product of **4**, *i.e.*, the monocarboxylic acid (**5b**), were synthesized by the method described in our previous report.[4]

Some modifications of the acetate moiety of **3** were attempted next. The alkylation of **3a**

was performed by treating **3a** with one equivalent of *tert*-BuOK followed by MeI at room temperature to give the propionate derivative (**9**). By a similar reaction, **9** was converted into the 2-methylpropionate derivative (**10**).

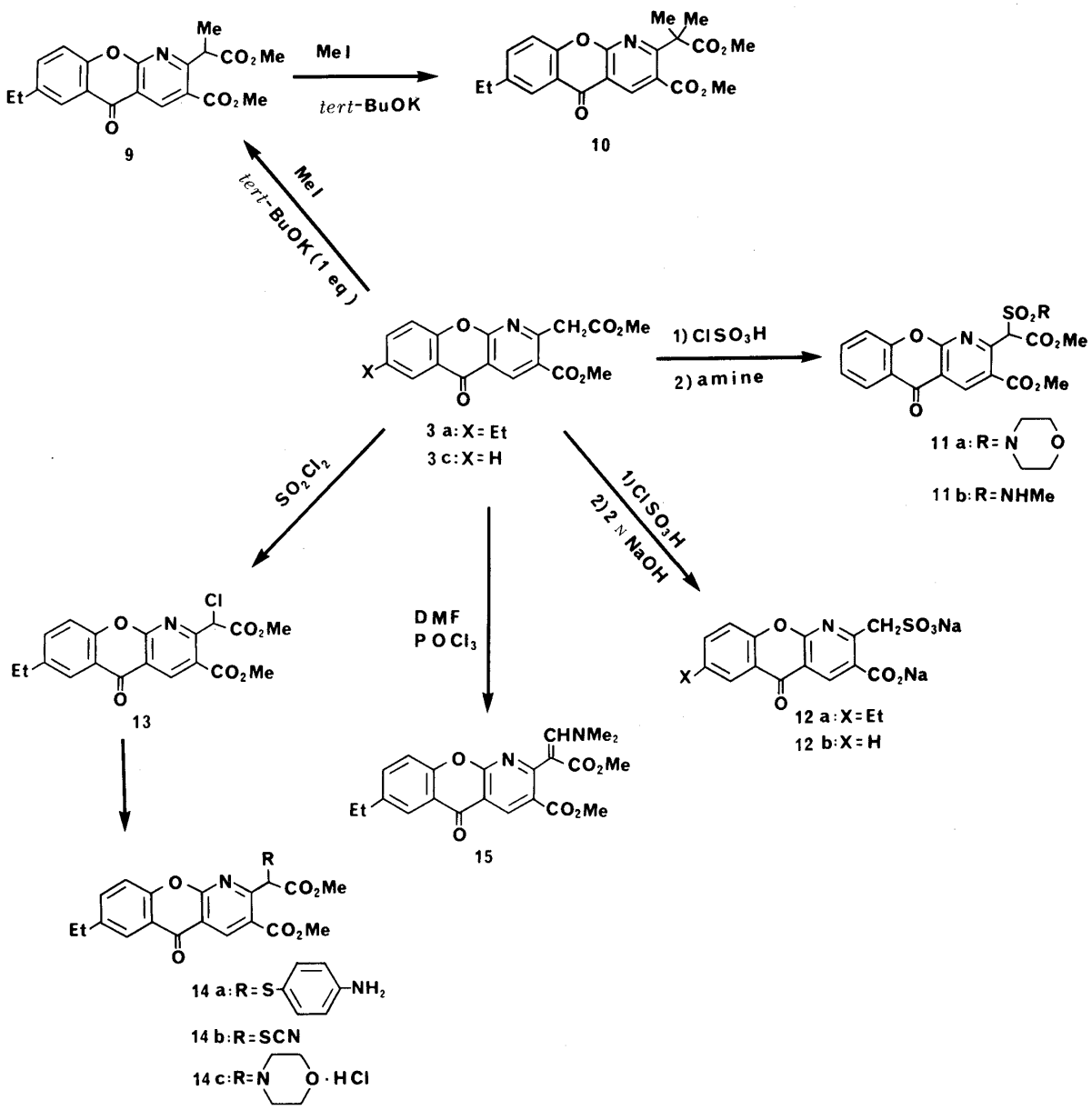


Chart 2

Sulfonamide (**11**) and methanesulfonate (**12**) derivatives were obtained by reacting **3** with chlorosulfonic acid followed by amination or by hydrolysis with 2 N NaOH. To introduce sulfide or amino groups into the acetate moiety, **3** was chlorinated with sulfuryl chloride to give **13**, which upon treatment with 4-mercaptoaniline, morpholine or sodium thiocyanate afforded **14a**—**c**. The reaction of **3a** with dimethylformamide (DMF)–$POCl_3$ gave the dimethylaminomethylidene derivative (**15**).

The oxime derivative (**16**) was formed by the reaction of **3c** with isoamyl nitrite in 85% H_2SO_4, but it could not be isolated in a pure state because it partially decomposed during chromatography on silica gel or recrystallization. Compound **16** was also obtained in low yield by condensing **2c** with the oxime derivative (**17**), which was prepared by a similar oximation of dimethyl 1,3-acetonedicarboxylate. When **16** was heated above its melting point,

it cyclized into the 1,2-oxazine derivative (**18**).

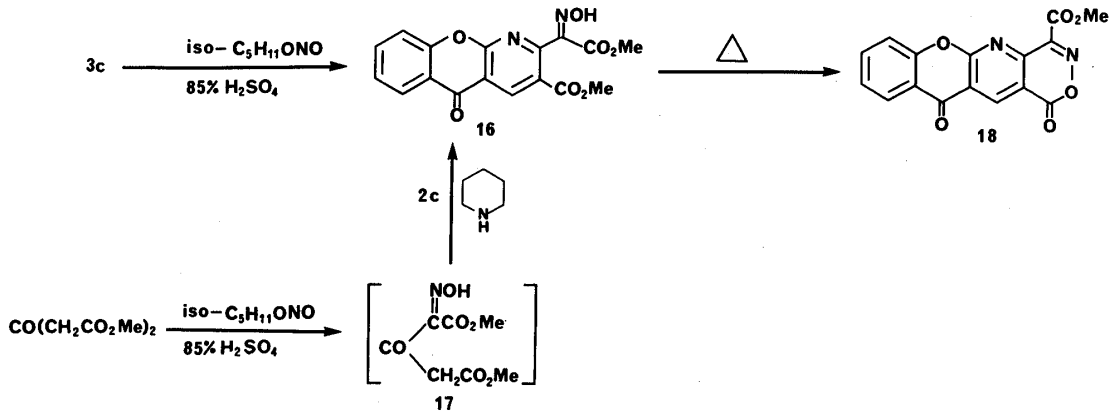


Chart 3

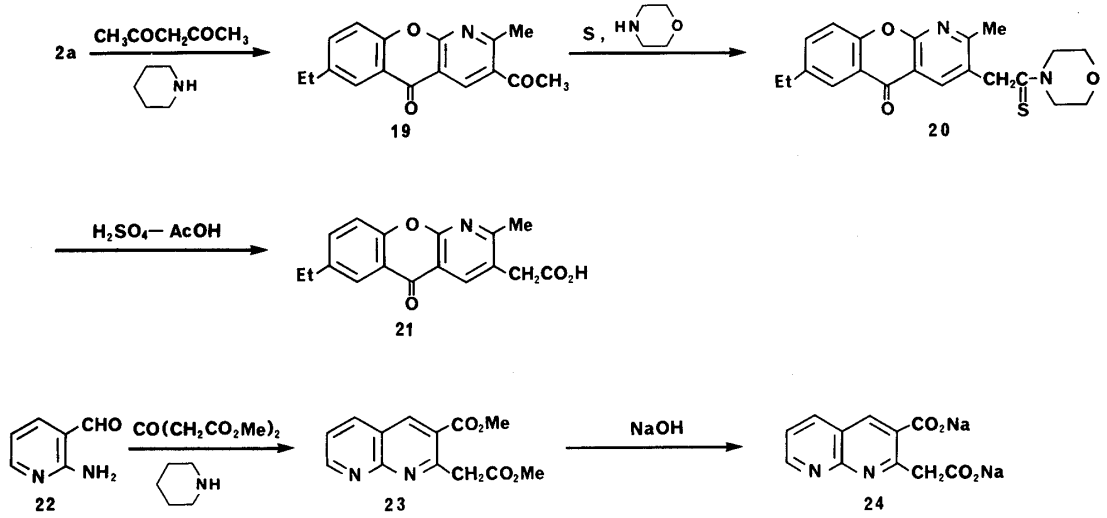


Chart 4

5-Oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine derivatives carrying an acetic acid group at the 3-position (**21**), and a naphthyridine derivative (**24**) in which the chromone ring of **4** was replaced by a pyridine nucleus were synthesized as related compounds. The 3-acetyl derivative (**19**), prepared by condensing **2a** with acetylacetone, was heated with sulfur and morpholine to give the thioacetamide derivative (**20**), which upon hydrolysis afforded the desired **21**. Compound **24** was prepared by hydrolyzing the ester derivative **23**, synthesized from 2-aminonicotinaldehyde (**22**)[7] and dimethyl 1,3-acetonedicarboxylate.

Pharmacology

The compounds listed in Table I were screened in the rat adjuvant arthritis assay.[8] In addition, the effects on the increase in body weight (difference between body weight measured after 14 d and on the day of sensitization) and the weight of the thymus were investigated.

The biological effects of representative compounds are shown in Table II. Compounds **3b**, **3m**,[9] **3n**, **4a**, and **4b** not only improved the systemic inflammation score and corrected the restraint on the increase in body weight induced by adjuvant arthritis but also increased the weight of the thymus. In addition, they did not exhibit antiinflammatory activity in the rat carrageenin-induced edema method at 200 mg/kg, *p.o.* or analgesic activity in the mouse phenylquinone writhing method at 200 mg/kg, *p.o.*; nor did they show ulcerogenicity at 2 g/kg, *p.o.* or have any effect on prostaglandin synthetase originating from the bovine seminal vesicle

TABLE II. Effect of (3-Carboxy-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridin-2-yl)acetic Acid Derivatives on Rat Adjuvant Arthritis[a)]

Entry	Compd.[b)]	Systemic inflammation score	Weight of thymus (mg)	Increase in body weight (g)
1	Control	8.8 ±0.7	211.7±21.5	42.2±2.5
	4a	4.7 ±1.6[c)]	375 ±52.0[c)]	50.0±3.1
2	Control	7.2 ±0.8	260.0±30.7	34.2±6.3
	4b	3.8 ±0.5[d)]	338.8±57.1	36.0±4.7
3	Control	8.67±0.92	275.5±35.3	28.7±3.5
	3b	3.67±1.02[d)]	395.7±37.6[c)]	43.0±6.4
4	Control	8.0 ±0.5	286.5±34.3	42.5±3.2
	3m	4.0 ±1.0[d)]	444.2±69.9	43.3±8.6
	3n	4.0 ±1.1[c)]	410.3±60.4	47.2±8.1

a) 14 d after sensitization. *b*) Dose: 50 mg/kg/d, *p.o.* *c*) $p<0.05$. *d*) $p<0.01$.

(10^{-4} M).

However, the biological results of the related compounds showed that there are rather severe structural requirements for the activity: compound **5b** (decarboxylated product of **4a**), **6** and **7** (the acetate moiety of **4** was replaced with a propionic acid group), **8** (the methylene group of **4** was absent), **9** and **10** (the acetic acid moiety was converted to a propionic acid group), **12** (the carboxy group was replaced with sulfonic acid), and the acetic acid derivatives (**21** and **24**) were weakly active or almost inactive.

Experimental

Melting points were determined on a micromelting point apparatus (Yanagimoto) and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on Varian T-60 and Varian EM-390 high resolution NMR spectrometers with tetramethylsilane as an internal or external standard. Infrared (IR) spectra were recorded on a Hitachi 215 grating infrared spectrophotometer.

Methyl (7-Ethyl-3-methoxycarbonyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridin-2-yl)acetate (3a) and Methyl 7-Ethyl-2-methyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carboxylate (5a)——A mixture of 6-ethyl-4-oxo-4*H*-1-benzopyran-3-carbonitrile (**2a**)[5)] (1.99 g, 10 mmol), dimethyl 1,3-acetonedicarboxylate, and piperidine (0.2 ml) in MeOH (20 ml) was refluxed for 3 h. The mixture was concentrated *in vacuo*, and the crystalline residue was chromatographed on silica gel. The first eluate with hexane–chloroform-ethyl acetate (10 : 10 : 1) gave **5a** as colorless crystals (10 mg), mp 148—150 °C. IR (KBr): 1730, 1665, 1615, 1605 cm^{-1}. NMR (in $CDCl_3$) δ: 1.30 (3H, t, $J=7$ Hz, Me), 2.77 (2H, q, $J=7$ Hz, CH_2), 2.96 (3H, s, Me), 3.95 (3H, s, OMe), *ca.* 7.45 (2H, m, $H_{8,9}$), 7.98 (1H, br s, H_6), 9.07 (1H, s, H_4). The second eluate was concentrated *in vacuo*, and the residue was recrystallized from MeOH to give **3a** as pale yellow needles (1.04 g, 29%), mp 142—143 °C. IR (KBr): 1740, 1710, 1660 cm^{-1}. NMR (in $CDCl_3$) δ: 1.30 (3H, t, $J=7$ Hz, Me), 2.78 (2H, q, $J=7$ Hz, Me), 3.70 (3H, s, OMe), 3.93 (3H, s, OMe), 4.36 (2H, s, CH_2), 7.42 (1H, d, $J=9$ Hz, H_9), 7.60 (1H, dd, $J=2$, 9 Hz, H_8), 8.03 (1H, br s, H_6), 9.20 (1H, s, H_4).

Ethyl (3-Ethoxycarbonyl-7-ethyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridin-2-yl)acetate (3m)——A mixture of diethyl 1,3-acetonedicarboxylate (8.8 g, 43.5 mmol), **2a** (8.00 g, 40 mmol), and piperidine (0.5 ml) in EtOH (70 ml) was refluxed for 2 h, then cooled. The crystals formed were collected by filtration, and recrystallized from EtOH, giving crude **3m** (14.8 g), mp 119—120 °C. It was chromatographed on silica gel (hexane–chloroform–acetone–formic acid (20 : 20 : 1 : 0.05)), and recrystallized from EtOH to give pure **3m** as colorless needles (5.49 g, 35.8%), mp 123—124 °C, and **3m** including a trace amount of impurity (6.59 g, 43.0%). IR (KBr): 1725, 1670, 1615, 1605 cm^{-1}. NMR (in $CDCl_3$) δ: 1.25 (3H, t, $J=7$ Hz, Me), 1.30 (3H, t, $J=7$ Hz, Me), 1.43 (3H, t, $J=7$ Hz, Me), 2.78 (2H, q, $J=7$ Hz, CH_2), 4.17 (2H, q, $J=7$ Hz, OCH_2), 4.36 (1H, s, CH_2CO), 4.40 (2H, q, $J=7$ Hz, OCH_2), 7.43 (1H, d, $J=9$ Hz, H_9), 7.58 (1H, dd, $J=2$, 9 Hz, H_8), 8.03 (1H, br s, H_6), 9.19 (1H, s, H_4).

Ethyl (7-Acetyl-3-ethoxycarbonyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridin-2-yl)acetate (3o)——Jones reagent (4.0 ml), prepared from CrO_3 (6.0 g), 97% H_2SO_4 (3.6 ml), and H_2O (18 ml), was added to a solution of ethyl [3-ethoxycarbonyl-7-(1-hydroxyethyl)-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridin-2-yl]acetate (**3l**) (3.99 g, 10 mmol) in

acetone (50 ml) over a period of 20 min at room temperature, and H_2O (150 ml) was added to the reaction mixture. The separated crystals were collected by filtration, chromatographed on silica gel (chloroform–acetone–formic acid (80 : 1 : 0.1)), and recrystallized from AcOEt to give **3o** as colorless needles (3.14 g, 79%), mp 160—161 °C. IR (KBr): 1735 (sh), 1730, 1720, 1685, 1670, 1610, 1605 cm^{-1}. NMR (in $CDCl_3$) δ: 1.28 (3H, t, J=7 Hz, Me), 1.46 (3H, t, J=7 Hz, Me), 2.71 (3H, s, Ac), 4.19 (2H, q, J=7 Hz, CH_2), 4.38 (2H, s, CH_2), 4.45 (2H, q, J=7 Hz, OCH_2), 7.47 (1H, d, J=9 Hz, H_9), 8.38 (1H, dd, J=2, 9 Hz, H_8), 8.82 (1H, d, J=2 Hz, H_6), 9.33 (1H, s, H_4).

Disodium (3-Carboxylate-7-ethyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridin-2-yl)acetate (4a)——A mixture of **3a** (7.10 g, 20 mmol) and 1 N NaOH (42 ml) in THF (100 ml) was stirred at room temperature for 2 h. MeOH (200 ml) was added, and the precipitated crystals were collected by filtration, recrystallized from H_2O–MeOH, and dried *in vacuo* at 50 °C to give **4a** as colorless crystals (6.5 g, 80%), mp 275—280 °C (dec.). IR (KBr): 3370, 1660, 1610, 1580 cm^{-1}. NMR (in D_2O) δ: 1.04 (3H, t, J=7 Hz, Me), 2.38 (2H, q, J=7 Hz, CH_2), 4.13 (2H, s, CH_2CO), 6.83 (1H, d, J=9 Hz, H_9), 7.10 (1H, dd, J=2, 9 Hz, H_8), 7.20 (1H, s, overlap, H_6), 8.36 (1H, s, H_4).

Ethyl 3-(3-Ethoxycarbonyl-7-ethyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridin-2-yl)propionate (6a)——A mixture of **2a** (1.99 g, 10 mmol), diethyl β-ketoadipate[6] (2.0 g, 9.3 mmol), and piperidine (0.3 ml) in EtOH (15 ml) was refluxed for 1.5 h, and cooled to room temperature. The precipitated crystals were collected by filtration, suspended in EtOH, refluxed, and then cooled. The resulting crystals were collected by filtration to give **6a** as colorless long needles (1.93 g, 48.6%), mp 168—170 °C. IR (KBr): 1730, 1720, 1670 cm^{-1}. NMR (in $CDCl_3$) δ: 1.27 (3H, t, J=7 Hz, Me), 1.32 (3H, t, J=7 Hz, Me), 1.45 (3H, t, J=7 Hz, Me), 2.78 (2H, q, J=7 Hz, CH_2), 2.90 (2H, t, J=7 Hz, $COCH_2$), 3.66 (2H, t, J=7 Hz, CH_2), 4.15 (2H, q, J=7 Hz, OCH_2), 4.42 (2H, q, J=7 Hz, OCH_2), 7.45 (1H, d, J=9 Hz, H_9), 7.62 (1H, dd, J=2, 9 Hz, s, H_8), 8.07 (1H, br s, H_6), 9.14 (1H, s, H_4).

3-(3-Carboxy-7-ethyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridin-2-yl)propionic Acid (7a)——A mixture of **6a** (2.6 g, 6.65 mmol), 80% H_2SO_4 (16 ml), and AcOH (4 ml) was stirred at 70 °C. After the solution had become clear H_2O (8 ml) was added over a period of 20 min, and the mixture was heated at 100 °C for 2 h. Water was added, and the resulting precipitate was collected by filtration and washed with water. The precipitate was dissolved in 1 N NaOH (45 ml) and stirred at room temperature for 1.5 h, then the solution was acidified with concentrated HCl. The resulting precipitate was collected by filtration and recrystallized from DMF–H_2O to give **7a** as colorless fine crystals (2.01 g, 88.7%), mp 284—287 °C (dec.). IR (KBr): 2960—2200, 1700—1690, 1670, 1280, 1215 cm^{-1}. NMR (in DMSO-d_6) δ: 1.43 (3H, t, J=7 Hz, Me), 2.47—2.97 (4H, m, CH_2, CH_2), 3.50 (2H, t, J=7 Hz, CH_2), 7.47—7.80 (2H, m, $H_{8,9}$), 7.92 (1H, br s, H_6), 8.90 (1H, s, H_4), 12.87 (2H, br, OH).

Methyl 2-(7-Ethyl-3-methoxycarbonyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridin-2-yl)propionate (9)——*tert*-BuOK (1.20 g, 10.7 mmol) was added to a solution of **3a** (3.55 g, 10 mmol) in THF (50 ml) and the mixture was stirred at room temperature for 10 min. MeI (5 ml) was added and the reaction mixture was allowed to stand at room temperature for 60 h. An inorganic salt was filtered off and the filtrate was concentrated *in vacuo*. The residue was recrystallized from $CHCl_3$–MeOH to give **9** as colorless needles (3.05 g, 82.6%), mp 131—133 °C. Further purification by silica gel chromatography (hexane–chloroform–acetone (30 : 10 : 2)) and recrystallization from $CHCl_3$–MeOH gave **9** as colorless crystals, mp 137—139 °C. IR (KBr): 1735, 1725, 1670 cm^{-1}. NMR (in $CDCl_3$) δ: 1.31 (3H, t, J=7 Hz, Me), 1.68 (3H, d, J=7 Hz, Me), 2.80 (2H, q, J=7 Hz, CH_2), 3.70 (3H, s, OMe), 3.96 (3H, s, OMe), 5.00 (1H, q, J=7 Hz, CH), 7.53 (1H, d, J=9 Hz, H_9), 7.66 (1H, dd, J=2, 9 Hz, H_8), 8.11 (1H, d, J=2 Hz, H_6), 9.27 (1H, s, H_4). *Anal.* Calcd for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.19; N, 3.79. Found: C, 64.81; H, 5.14; N, 3.64.

Methyl 2-(7-Ethyl-3-methoxycarbonyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridin-2-yl)-2-methylpropionate (10)——*tert*-BuOK (1.08 g, 9.64 mmol) was added to a solution of **9** (3.33 g, 9.02 mmol) in THF (30 ml) and the mixture was stirred at room temperature. After 5 min, MeI (5 ml) was added and the whole was stirred for 30 min. The resulting precipitate was filtered off and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography (chloroform–acetone (200 : 1)) and recrystallized from MeOH to give **10** as colorless crystals (2.46 g, 71.1%), mp 93—94 °C. IR (KBr): 1755, 1745, 1735—1720, 1675, 1670 cm^{-1}. NMR (in $CDCl_3$) δ: 1.33 (3H, t, J=7 Hz, Me), 1.76 (6H, s, Me, Me), 2.86 (2H, q, J=7 Hz, CH_2), 3.68 (3H, s, OMe), 3.93 (3H, s, OMe), *ca.* 7.58 (2H, m, $H_{8,9}$), 8.11 (1H, br s, H_6), 9.17 (1H, s, H_4). *Anal.* Calcd for $C_{21}H_{21}NO_6$: C, 65.78; H, 5.52; N, 3.65. Found: C, 65.80; H, 5.42; N, 3.68.

Methyl 2-(3-Methoxycarbonyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridin-2-yl)-2-morpholinosulfonylacetate (11a)——$ClSO_3H$ (2.4 ml, 36.3 mmol) was added to a solution of **3c** (6 g, 18.3 mmol) in $CHCl_3$ (60 ml) and the mixture was refluxed for 80 h. A solution of morpholine (3.5 ml, 40 mmol) in $CHCl_3$ (6 ml) was added to the reaction mixture over a period of 10 min under ice-cooling and the whole was stirred at room temperature for 1 h, then concentrated. Water (100 ml) was added, and the resulting precipitate was collected by filtration and recrystallized from $CHCl_3$–DMSO to give **11a** as colorless needles (5.7 g, 62%), mp 187—190 °C (dec.). IR (KBr): 3757, 3520, 1745, 1720, 1668, 1610, 1600 cm^{-1}. NMR (in DMSO-d_6) δ: 3.0—3.2 (4H, m), 3.68 (3H, s), 3.65—3.9 (4H, m), 3.89 (3H, s), 6.31 (1H, s), 7.4—8.05 (3H, m), 8.15 (1H, dd, J=2, 8 Hz), 8.80 (1H, s). *Anal.* Calcd for $C_{21}H_{20}N_2O_9S \cdot 3/2H_2O$: C, 50.10; H, 4.60; N, 5.56. Found: C, 50.33; H, 4.48; N, 5.57.

Methyl 2-(3-Methoxycarbonyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridin-2-yl)-2-*N*-methylsulfamoylacetate (11b)——This compound (**11b**) was prepared as described for **11a**. Recrystallization from H_2O–MeOH gave **11b** as a pale bluish green powder (45.9%), mp 177—181 °C (dec). IR (KBr): 3650—2650, 1740, 1720, 1675, 1610, 1600 cm^{-1}.

NMR (in DMSO-d_6) δ: 2.27—2.55 (3H, m), 3.70 (3H, s), 3.90 (3H, s), 6.34 (1H, s), 7.4—8.2 (4H, m), 8.80 (1H, s). *Anal.* Calcd for $C_{18}H_{16}N_2O_8S \cdot 3/2H_2O$: C, 48.32; H, 4.28; N, 6.26. Found: C, 48.60; H, 4.22; N, 6.28.

Disodium (5-Oxo-2-sulfonatomethyl-5*H*-[1]benzopyrano[2,3-*b*]pyridin-3-yl)carboxylate (12b)——A solution of $ClSO_3H$ (2.0 ml, 30.5 mmol) in $CHCl_3$ (5 ml) was added to a solution of **3c** (4 g, 12.2 mmol) in $CHCl_3$ (30 ml) over a period of 1 h under refluxing. The mixture was refluxed for an additional 2 h and cooled to room temperature. A mixture of H_2O (2 ml) and MeOH (8 ml) was added over a period of 5 min, and the reaction mixture was stirred at room temperature for 30 min. The solvent was evaporated off *in vacuo* and the residue was dissolved in 2 N NaOH (40 ml). The mixture was stirred at room temperature for 5 h. EtOH (300 ml) was added and the precipitated crystals were collected by filtration, and dissolved in H_2O (30 ml), then the solution was acidified with concentrated HCl (6 ml). The crystals were collected by filtration, and dissolved in 1 N NaOH (30 ml). EtOH (200 ml) was added to the solution and the crystals were collected by filtration then recrystallized from H_2O–EtOH to give **12b** as pale yellow needles (3.069 g, 63.3%), mp > 300 °C. IR (KBr): 3650—2900, 1670, 1615, 1600 cm^{-1}. NMR (in D_2O) δ: 5.19 (2H, s), 7.28—8.10 (4H, m), 8.75 (1H, s). *Anal.* Calcd for $C_{14}H_7NNa_2O_7S \cdot H_2O$: C, 42.32; H, 2.28; N, 3.53. Found: C, 42.50; H, 2.55; N, 3.28.

Disodium (7-Ethyl-5-oxo-2-sulfonatomethyl-5*H*-[1]benzopyrano[2,3-*b*]pyridin-3-yl)carboxylate (12a)——This compound (**12a**) was prepared as described for **12b**. Recrystallization from H_2O–EtOH gave **12a** as a white powder (38.5%), mp 170 °C (dec.). IR (KBr): 3700—2700, 1665, 1610 cm^{-1}. NMR (in D_2O) δ: 1.16 (3H, t, J=7 Hz, Me), 2.50 (2H, q, J=7 Hz, CH_2), 5.01 (2H, s, CH_2SO_3), 7.05 (1H, d, J=8 Hz, H_9), 7.29 (1H, dd, J=2, 8 Hz, H_8), 7.43 (1H, d, J=2 Hz, H_6), 8.53 (1H, s, H_4). *Anal.* Calcd for $C_{16}H_{11}NNa_2O_7S \cdot 5/2H_2O$: C, 42.48; H, 3.57; N, 3.10. Found: C, 42.63; H, 3.64; N, 3.20.

Methyl 2-Chloro-2-(7-ethyl-3-methoxycarbonyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridin-2-yl)acetate (13)——A mixture of **3a** (7.10 g, 20 mmol) and SO_2Cl_2 (2.0 ml, 24.7 mmol) in CCl_4 (100 ml) was refluxed for 30 min and a small amount of precipitate was removed by filtration. The filtrate was evaporated to dryness, EtOH (*ca.* 20 ml) was added to the residue, and the crystals were collected by filtration to give **13** as colorless crystals (6.25 g, 80%), mp 147—149 °C. Further purification by silica gel chromatography (hexane–chloroform–acetone–formic acid (20 : 20 : 1 : 0.05)) and recrystallization from EtOH gave colorless crystals, mp 148—150 °C. IR (KBr): 1765, 1715, 1670 cm^{-1}. NMR (in $CDCl_3$) δ: 1.31 (3H, t, J=7 Hz, Me), 2.78 (2H, q, J=7 Hz, CH_2), 3.85 (3H, s, OMe), 3.99 (3H, s, OMe), 6.67 (1H, s, CHCl), 7.44 (1H, d, J=9 Hz, H_9), 7.61 (1H, dd, J=2, 9 Hz, H_8), 8.03 (1H, br s, H_6), 9.24 (1H, s, H_4). *Anal.* Calcd for $C_{19}H_{16}ClNO_6$: C, 58.55; H, 4.14; N, 3.59. Found: C, 58.69; H, 4.16; N, 3.65.

Methyl 2-(4-Aminophenylthio)-2-(7-ethyl-3-methoxycarbonyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridin-2-yl)-acetate (14a)——A mixture of **13** (3.89 g, 10 mmol), 4-aminothiophenol (1.25 g, 10 mmol) and Et_3N (1 ml) in $CHCl_3$ (20 ml) was stirred at room temperature for 30 min, and the solvent was evaporated off *in vacuo*. The residue was heated with EtOH, and insoluble material was collected by filtration while the mixture was hot. The solid was chromatographed on silica gel (chloroform–acetone–formic acid (20 : 1 : 0.1)), and recrystallized from $CHCl_3$–acetone to give **14a** as yellow crystals (3.43 g, 71.7%), mp 174—176 °C. IR (KBr): 3460, 3360, 1750, 1730, 1665 cm^{-1}. NMR (in $CDCl_3$) δ: 1.30 (3H, t, J=7 Hz, Me), 2.78 (2H, q, J=7 Hz, CH_2), *ca.* 3.40 (2H, br, NH_2), 3.73 (3H, s, OMe), 3.88 (3H, s, OMe), 5.98 (1H, s, $CHCO_2$), 6.48 (2H, d, J=8 Hz, phenyl), 7.19 (2H, d, J=8 Hz, phenyl), 7.45 (1H, d, J=9 Hz, H_9), 7.60 (1H, dd, J=2, 9 Hz, H_8), 8.05 (1H, br s, H_6), 9.15 (1H, s, H_4). *Anal.* Calcd for $C_{25}H_{22}N_2O_6S$: C, 62.75; H, 4.64; N, 5.85. Found: C, 62.46; H, 4.61; N, 5.92.

Methyl 2-Thiocyanato-2-(7-ethyl-3-methoxycarbonyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridin-2-yl)acetate (14b)——A mixture of **13** (1.95 g, 5 mmol) and NaSCN (567 mg, 7 mmol) in DMF (5 ml) was stirred at 100 °C for 1 h. The reaction mixture was diluted with water, extracted with AcOEt, dried (Na_2SO_4), and concentrated. The separated crystals were collected by filtration and recrystallized from $CHCl_3$–AcOEt to give **14b** as colorless plates (1.34 g, 65.0%), mp 168—170 °C (dec.). IR (KBr): 2150 (CN), 1740, 1710, 1670 cm^{-1}. NMR (in $CDCl_3$) δ: 1.30 (3H, t, J=7 Hz), 2.83 (2H, q, J=7 Hz), 3.83 (3H, s), 3.97 (3H, s), 6.33 (1H, s), 7.46 (1H, d, J=9 Hz), 7.62 (1H, dd, J=2, 9 Hz), 8.03 (1H, d, J=2 Hz), 9.31 (1H, s). *Anal.* Calcd for $C_{20}H_{16}N_2O_6S$: C, 58.25; H, 3.91; N, 6.79. Found: C, 58.15; H, 4.11; N, 6.85.

Methyl 2-(7-Ethyl-3-methoxycarbonyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridin-2-yl)-2-morpholinoacetate Hydrochloride (14c)——A mixture of **13** (1.55 g, 4 mmol) and morpholine (0.68 ml, 8 mmol) in $CHCl_3$ (8 ml) was refluxed for 25 h. After removal of the solvent, the residue was dissolved into AcOEt, washed with water, and dried (Na_2SO_4). The solvent was evaporated off *in vacuo* and the residue was chromatographed on silica gel (chloroform–acetone–formic acid (30 : 1 : 0.1)). HCl–MeOH was added to the residual oil, and the MeOH was evaporated off. The residue was recrystallized from MeOH–ether to give **14c** as colorless fine crystals (950 mg, 49.8%), mp 128—132 °C. IR (KBr): 2500—2100, 1755, 1730, 1675, 1665, 1600 cm^{-1}. NMR (in DMSO-d_6) δ: 1.26 (3H, t, J=7 Hz), 2.78 (2H, q, J=7 Hz), *ca.* 3.13 (4H, br), *ca.* 3.7 (4H, br), 3.73 (3H, s), 3.95 (3H, s), 6.18 (1H, s), *ca.* 7.00 (*ca.* 2H, br), 7.60 (1H, d, J=9 Hz), 7.75 (1H, overlap), 7.90 (1H, br s), 8.93 (1H, s). *Anal.* Calcd for $C_{23}H_{24}N_2O_7 \cdot HCl$: C, 57.92; H, 5.28; N, 5.87. Found: C, 58.29; H, 4.84; N, 5.76.

Methyl 2-(Dimethylaminomethylidene)-2-(7-ethyl-3-methoxycarbonyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridin-2-yl)acetate (15)——A mixture of **3a** (2.0 g, 5.63 mmol) and $POCl_3$ (2 ml) in DMF (20 ml) was heated at 80 °C for 5 min and the resulting solution was allowed to stand at room temperature for 30 min. The reaction mixture was

poured into ice-water, and the yellow precipitate was collected, then dissolved in AcOEt. The solution was washed with water and dried (Na_2SO_4), and the solvent was evaporated off. The residue was chromatographed on silica gel (chloroform–acetone–formic acid (20 : 1 : 0.1)) and recrystallized from AcOEt (trace)—iso-Pr_2O to give **15** as yellow needles (930 mg, 40.3%), mp 163—165 °C. IR (KBr): 1730, 1690, 1665, 1600 cm^{-1}. NMR (in $CDCl_3$) δ: 1.32 (3H, t, J=7 Hz), 2.80 (2H, q, J=7 Hz), 2.93 (6H, s), 3.62 (3H, s), 3.89 (3H, s), 7.43 (1H, d, J=9 Hz), 7.60 (1H, dd, J=2, 9 Hz), 7.74 (1H, s), 8.07 (1H, d, J=2 Hz), 9.00 (1H, s). *Anal.* Calcd for $C_{22}H_{22}N_2O_6$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.11; H, 5.41; N, 6.61.

Methyl 2-(Hydroxyimino)-2-(3-methoxycarbonyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridin-2-yl)acetate (16)——Method A: Under ice-salt cooling, isoamyl nitrite (2.96 ml, 22 mmol) was added to a solution of **3c** (2.97 g, 9.1 mmol) in 85% H_2SO_4 (10 ml) at 0—5 °C over a period of 1 h. The reaction mixture was poured into ice-water, extracted with AcOEt and dried (Na_2SO_4). After removal of the solvent, the residue was chromatographed on silica gel (chloroform–acetone–formic acid (9 : 1 : 0.1)). The first fraction gave the starting material **3c** (910 mg, 30.6%). The second fraction gave colorless crystals (840 mg), which were rechromatographed. Recrystallization from $CHCl_3$–EtOH gave crude **16** as colorless crystals (610 mg), mp 173—176 °C (dec.). (**16** was contaminated with a by-product formed during chromatography or recrystallization.) IR (KBr): 3400 (OH), 1745, 1730, 1675 cm^{-1}. NMR (in DMSO-d_6) δ: 3.77 (3H, s), 3.86 (3H, s), 7.28—7.92 (3H, m), 8.08 (1H, dd, J=2, 8 Hz), 8.93 (1H, s), 12.64 (1H, s, disappeared on adding D_2O).

Method B: Under ice-salt cooling, isoamyl nitrite (1.47 g) was added to a solution of dimethyl 3-oxoglutarate (1.74 g, 10 mmol) in 85% H_2SO_4 (2 ml) at −2—−1 °C over a period of *ca.* 30 min. The reaction mixture was stirred at 0—2 °C for 30 min, poured into ice-water, extracted with AcOEt, washed with water, and dried (Na_2SO_4). The solvent was removed, and the resulting oil was chromatographed on silica gel (chloroform–acetone–formic acid (9 : 1 : 0.1)) to give dimethyl 2-hydroxyimino-3-oxoglutarate (**17**) (700 mg). A mixture of **17** (700 mg), **2c** (600 mg), and piperidine (0.1 ml) in MeOH (6 ml) was refluxed for 2 h and cooled to room temperature. The precipitate was collected and recrystallized from $CHCl_3$–EtOH to give **16** as pale brown crystals (230 mg), mp 173—176 °C (dec.). The infrared spectrum was identical with that of **16** prepared by method A.

Methyl 1,11-Dioxo-benzopyrano[2′,3′-2,3]pyridin[6,5-*d*]1,2-oxazine-4-carboxylate (18)——When **16** (220 mg) was heated above its melting point in a microtube, effervescence and then solidification occurred. $CHCl_3$ was added, and the resulting solid was collected, chromatographed on silica gel (chloroform–acetone–formic acid (50 : 1 : 0.1)), and recrystallized from $CHCl_3$–EtOH to give **18** as colorless crystals (120 mg) mp 248—250 °C. IR (KBr): 1780, 1760, 1690, 1670 cm^{-1}. NMR (in DMSO-d_6) δ: 4.07 (3H, s), 7.33—7.97 (3H, m), 8.12 (1H, dd, J=2, 8 Hz), 9.04 (1H, s). *Anal.* Calcd for $C_{16}H_8N_2O_6$: C, 59.26; H, 2.49; N, 8.64. Found: C, 59.08; H, 2.37; N, 8.62.

3-Acetyl-7-ethyl-2-methyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine (19)——A mixture of **2a** (19.9 g, 0.1 mol), acetylacetone (11.0 g, 0.11 mol), and piperidine (2 ml) in EtOH (200 ml) was refluxed for 4 h and cooled. The separated crystals were collected and recrystallized from EtOH to give **19** as pale yellow crystals (15.46 g, 54.6%), mp 140—142 °C. IR (KBr): 1690, 1660 cm^{-1}. NMR (in $CDCl_3$) δ: 1.32 (3H, t, J=7 Hz), 2.60—3.03 (2H), 2.70 (3H, s), 2.86 (3H, s), 7.34—7.76 (2H, m), 8.04 (1H, m), 8.93 (1H, s). *Anal.* Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.68; H, 5.11; N, 5.01.

7-Ethyl-2-methyl-3-(4-morpholinothiocarbonylmethyl)-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine (20)——A mixture of **19** (11.24 g, 40 mmol), sulfur powder (2.10 g, 66 mmol), and morpholine (5.80 g, 66 mmol) was refluxed for 6 h. $CHCl_3$ was added to the hot reaction mixture, and the resulting solution was chromatographed on silica gel (chloroform and then chloroform–acetone–formic acid (20 : 1 : 0.1)). The eluate was concentrated and EtOH (300 ml) was added. The EtOH layer was removed by decantation and this procedure was repeated. The resulting black solid was collected, chromatographed on silica gel (chloroform–acetone–formic acid (20 : 1 : 0.1)), and recrystallized from $CHCl_3$–EtOH to give **20** as brown crystals (3.95 g, 25.8%), mp 209—211 °C. IR (KBr): 1645, 1605 cm^{-1}. NMR (in $CDCl_3$) δ: 1.28 (3H, t, J=7 Hz), 2.59 (3H, s), 2.77 (2H, q, J=7 Hz), 3.68 (4H, s), 3.83 (2H, t, J=5 Hz), 4.21 (2H, s), 4.42 (2H, t, J=5 Hz), 7.42 (1H, d, J=9 Hz), 7.58 (1H, dd, J=2, 9 Hz), 8.03 (1H, br s), 8.30 (1H, s). *Anal.* Calcd for $C_{21}H_{22}N_2O_3S$: C, 65.95; H, 5.80; N, 7.32. Found: C, 65.86; H, 5.49; N, 7.25.

(7-Ethyl-2-methyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridin-3-yl)acetic Acid (21)——A mixture of **20** (2 g, 5.23 mmol), AcOH (20 ml), and 6 N H_2SO_4 (20 ml) was refluxed for 10 h, and cooled to room temperature. The separated crystals were collected and washed with water. Recrystallization from DMF gave **21** as pale brown needles (1.43 g, 92%), mp 295—297 °C (dec.). IR (KBr): 1700, 1660, 1610 cm^{-1}. NMR (in DMSO-d_6) δ: 1.23 (3H, t, J=7 Hz), 2.48 (3H, s), 2.71 (2H, q, J=7 Hz), 3.78 (2H, s), 7.37 (1H, d, J=9 Hz), 7.57 (1H, dd, J=2, 9 Hz), 7.78 (1H, d, J=2 Hz), 8.23 (1H, s), *ca.* 12.3 (1H, br). *Anal.* Calcd for $C_{17}H_{15}NO_4$: C, 68.67; H, 5.08; N, 4.71. Found: C, 68.72; H, 5.22; N, 4.80.

Methyl (3-Methoxycarbonyl-1,8-naphthyridin-2-yl)acetate (23)——A mixture of 2-aminonicotinaldehyde (**22**)[7] (2.95 g, 24.18 mmol), dimethyl 1,3-acetone-dicarboxylate (7.2 ml), and piperidine (0.3 ml) in EtOH (35 ml) was refluxed for 6 h and insoluble material was removed by filtration. The filtrate was concentrated, and hexane was added. The solid was collected, chromatographed on silica gel (chloroform–acetone–formic acid (3 : 1 : 0.1)), and recrystallized from AcOEt to give **23** as crystals (3.25 g, 51.7%), mp 146—148 °C. IR (KBr): 1720, 1655, 1620 cm^{-1}. NMR (in $CDCl_3$) δ: 3.70 (3H, s), 3.95 (3H, s), 4.53 (2H, s), 7.51 (1H, dd, J=4, 8 Hz), 8.26 (1H, dd, J=2, 8 Hz), 8.85

(1H, s), 9.16 (1H, dd, $J=2$, 4 Hz). *Anal.* Calcd for $C_{13}H_{12}N_2O_4$: C, 59.99; H, 4.65; N, 10.77. Found: C, 60.16; H, 4.49; N, 11.08.

Disodium (3-Carboxylato-1,8-naphthyridin-2-yl)acetate (24)——A mixture of **23** (3.0 g, 11.5 mmol) and 1 N NaOH (15 ml) in THF (15 ml) was stirred at room temperature for 3 h, and concentrated. MeOH was added to the residue and the separated crystals were collected. They were recrystallized from H_2O–MeOH to give **24** as pale brown plates (1.26 g, 33.8%), mp >300 °C. IR (KBr): 1610, 1570, 850, 795 cm^{-1}. NMR (in D_2O) δ: 4.19 (2H, s), 7.43 (1H, dd, $J=4$, 8 Hz), 8.22 (1H, dd, $J=2$, 8 Hz), 8.33 (1H, s), 8.82 (1H, dd, $J=2$, 4 Hz). *Anal.* Calcd for $C_{11}H_6N_2Na_2O_4 \cdot 8/3H_2O$: C, 40.75; H, 3.52; N, 8.64. Found: C, 40.67; H, 3.69; N, 9.01.

Adjuvant Arthritis[8]——A suspension of killed *Mycobacteria butyricum* in liquid paraffin was injected subcutaneously into a hind-paw of male Sprague-Dawley rats (6 weeks old). The compounds, at a dose of 50 mg/kg in 4% gum arabic, were administered orally to rats at 0.5 ml per 100 g of body weight once a day for 14 consecutive days after injection of the adjuvant. The degree or severity of the inflammation induced on the hind-paw not injected with adjuvant, and on the front paws, tail, and ears was graded 1 to 5, and the grades were summed for each animal; the highest possible total for the four regions is 20.

References and Notes

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