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Synthesis of the Metabolites and Degradation Products of 2-Amino-7-isopropyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carboxylic Acid (Amoxanox)

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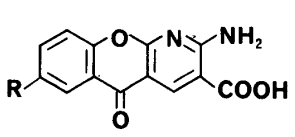
The metabolites and degradation products of 2-amino-7-isopropyl-5-oxo-5*H*-[1]benzopyrano-[2,3-*b*]pyridine-3-carboxylic acid (Amoxanox, AA-673, **1**), a promising drug for the treatment of bronchial asthma, were synthesized to confirm the proposed structures and to determine their activity in the rat passive cutaneous anaphylaxis test.

Keywords——antianaphylactic agent; 5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carboxylic acid; metabolite; degradation product

Since the introduction of disodium cromoglycate (DSCG) as a prophylactic agent for the treatment of bronchial asthma,[1] much effort has been devoted to finding new orally effective DSCG-like compounds inhibiting homologous passive cutaneous anaphylaxis (PCA) induced by reaginic antibody in the rat.[2] We found that 5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carboxylic acids and their tetrazole analogues inhibited the rat PCA reaction, and investigated the structure–activity relationship of these compounds.[3] After examination of the pharmacological and toxicological properties of these compounds, 2-amino-7-isopropyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carboxylic acid (Amoxanox, AA-673, **1**) was selected as the most promising drug, and its metabolic fate was investigated. In the metabolism study,[4] the 7-(1-hydroxy-1-methylethyl) derivative (**2**) and 7-(2-hydroxy-1-methylethyl) derivative (**3**) were proposed as metabolites of **1** in the plasma of rats and dogs. In man, **2** was the main metabolite. On the other hand, a stability study under severe test conditions[5] suggested that a 7-acetyl derivative (**4**) and a ring-opened compound (**5**) were the main degradation products formed by light and alkali, respectively. We synthesized compounds **2**—**5** to confirm the proposed structures and to determine their activity in the rat PCA test. The syntheses are described here.



1 R: $CH(CH_3)_2$
2 R: $C(CH_3)_2OH$
3 R: $CH(CH_3)CH_2OH$
4 R: $COCH_3$

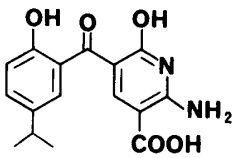


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Fig. 1

Syntheses of 2—5

First, we tried to prepare **2** from ethyl 2-amino-7-(1-hydroxy-1-methylethyl)-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carboxylate (**6**). Reaction of the ethyl ester of **1** (**7**)[3] with equimolar *N*-bromosuccinimide (NBS) followed by alkali treatment, or with NBS in the presence of H_2O in CCl_4, gave **6** only in a low yield. Therefore another route was tried. Bromination of 6-isopropyl-4-oxo-4*H*-1-benzopyran-3-carbonitrile (**9**)[6] with NBS gave the bromide (**10**) in a 48% isolation yield. Hydrolysis of **10** with 20% aqueous AcOH at 100 °C afforded the hydroxyl derivative (**8**) and the isopropenyl derivative (**11**) in 12% and 42% yields, respectively. On the other hand, hydrolysis of **10** with 1 N NaOH at room temperature gave **8** and **11** in 58% and 18% yields, respectively. The condensation of **8** with ethyl cyanoacetate in the presence of piperidine in EtOH gave **6** in 69% yield. Hydrolysis of **6** with 0.5 N NaOH in EtOH at 50 °C gave the desired **2** in 87% yield. Next we tried to prepare **2** in one step from **1**. Thus, oxidation of **1** with oxygen gas under infrared (IR) irradiation in 0.1 N NaOH at 70 °C gave **2** and the acetyl derivative (**4**) (see below) in 36% and 34% yields, respectively.

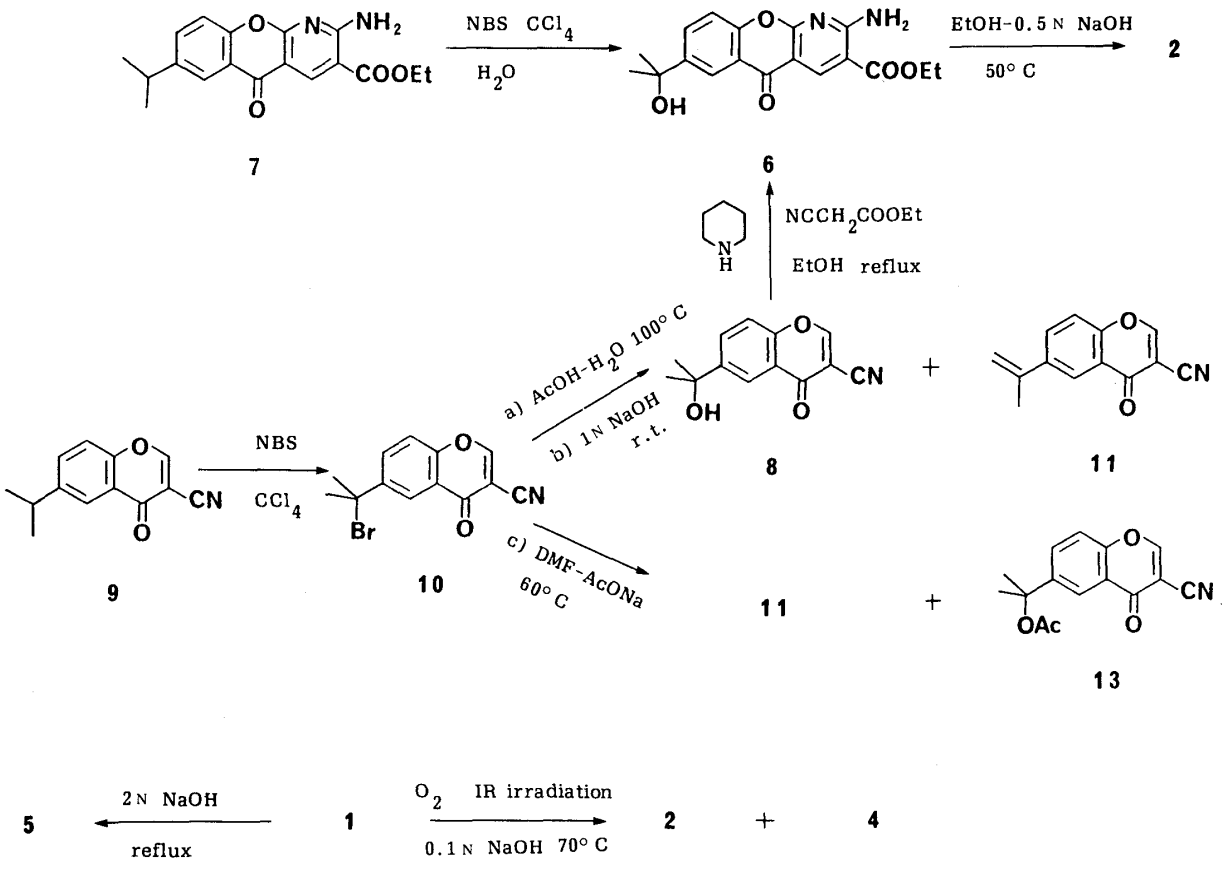

Chart 1

We regarded the epoxy derivative (**12**) as a key intermediate for the synthesis of **3** and examined methods for synthesizing **12**. Reaction of **10** with equimolar AcONa gave **11** in high yield (85%) together with a small amount of the acetoxy derivative (**13**, 5%). Oxidation of **11** with 40% CH_3CO_3H gave only the 2,3-epoxide (**14**), showing that the 2,3-double bond of the benzopyran ring is oxidized in preference to the isopropenyl group. Next, oxidation of the 7-isopropenyl-5-oxo-5*H*-[1]benzopyrano-[2,3-*b*]pyridine derivative (**15**) was attempted. Reaction of **15** with 40% CH_3CO_3H in the presence of NaOAc or *m*-chloroperbenzoic acid afforded the desired epoxide (**12**) in 55% yield together with a small amount of the acetyl

derivative (**16**, 6%) (see below). Catalytic hydrogenation of **12** in the presence of 5% Pd–C in THF–EtOH (3 : 1) gave the 7-(2-hydroxy-1-methylethyl) derivative (**17**) (61% yield), which was hydrolyzed to **3** (90% yield).

The 7-acetyl derivative (**4**) was synthesized by alkali hydrolysis of **16**, which was prepared from **18**.[7] The ring-opened derivative (**5**) was prepared from **1** by heating in 2 N NaOH.

These compounds (**2**—**5**) were confirmed to be identical with the metabolites and the degradation products of **1**.

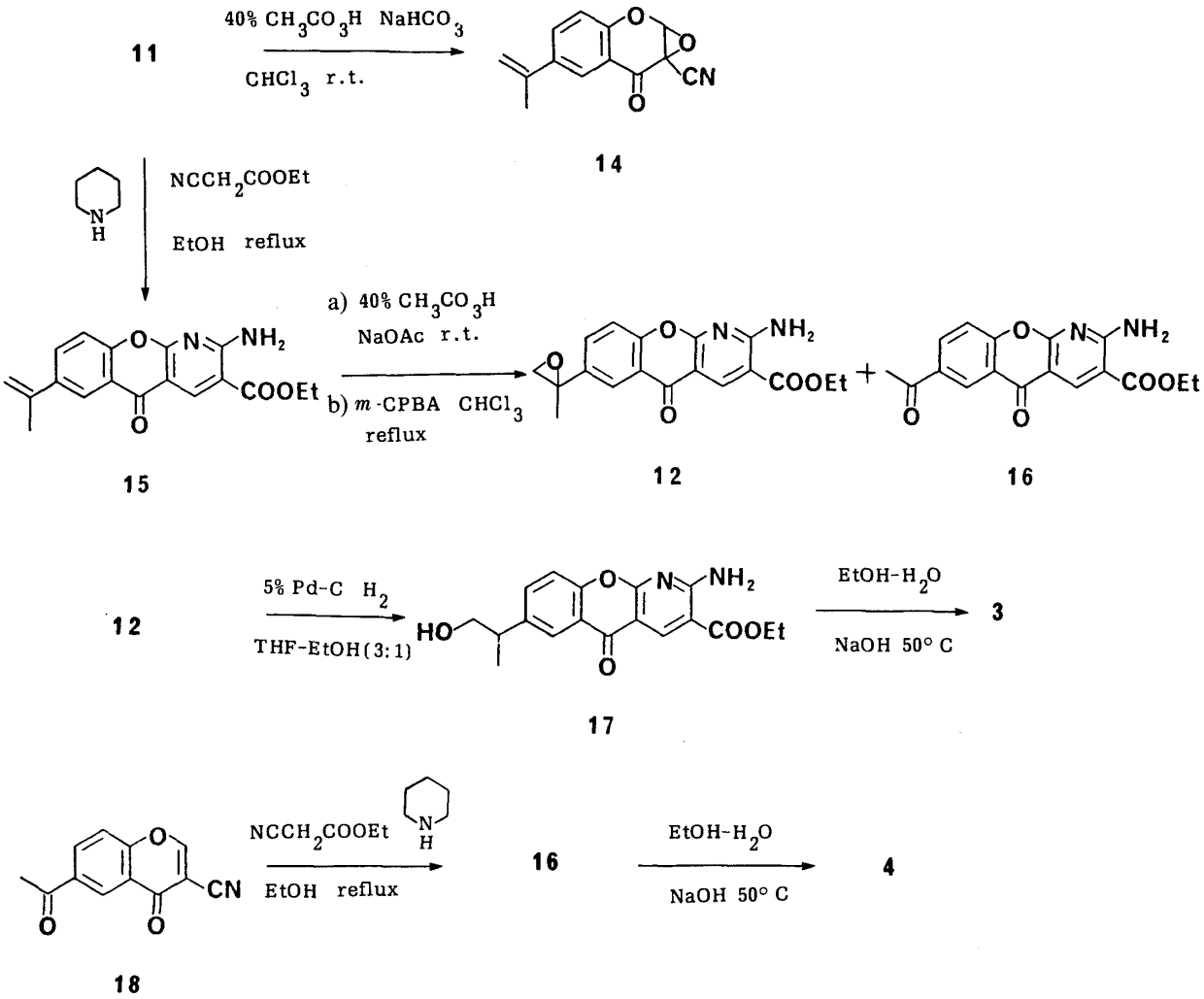

Chart 2

TABLE I. Inhibitory Effects of the Metabolites and Degradation Products of Amoxanox (**1**) on Passive Cutaneous Anaphylaxis in Rats

Compound	ID_{50} (mg/kg, *i.v.*)[a]
DSCG[b]	1.4 (1.3—1.6, 40)
1	0.032 (0.028—0.036, 40)
2	0.024 (0.019—0.029, 40)
3	0.0054 (0.0031—0.0074, 12)
4	0.020 (0.015—0.026, 9)
5	9.0 (7.6—11, 9)

a) ID_{50} = 50% inhibition dose. Numerals in parentheses are 95% confidence limits and number of rats used. *b*) Disodium cromoglycate.

The biological activity was measured by using the standard rat PCA tests as described in reference 7 and compared with that of DSCG. The results obtained after intravenous administration are shown in the table. Among the metabolites and degradation products, compound **3** was six times as potent as **1** and about 260 times as potent as DSCG. Compounds **2** and **4** showed activities comparable to that of **1**, while the ring-opened compound **5** showed reduced activity.

Experimental

All melting points were determined on a micro melting point apparatus (Yanagimoto) and are uncorrected. The following instruments were used to obtain physical data; nuclear magnetic resonance (NMR) spectra, Varian T-60 and EM-390 spectrometer; IR spectra, a Hitachi 215 grating infrared spectrophotometer; mass spectrum (MS), a Hitachi RMU-6D mass spectrometer. In the NMR spectra, chemical shifts are given on the δ (ppm) scale with tetramethylsilane as an internal standard, and coupling constants (J) are given in Hz. The following abbreviations are used: s = singlet, br s = broad singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet. IR light irradiation was conducted with a Toshiba infrared lamp, 100 V, 375WR.

6-(1-Bromo-1-methylethyl)-4-oxo-4*H*-1-benzopyran-3-carbonitrile (10)——A mixture of 6-isopropyl-4-oxo-4*H*-1-benzopyran-3-carbonitrile (**9**, 10.65 g, 50 mmol), NBS (8.90 g, 50 mmol), and CCl_4 (300 ml) was refluxed for 2 h under IR irradiation, then cooled to room temperature. The precipitate was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in AcOEt (150 ml) and the solution was washed with H_2O (50 ml × 3) and dried over anhydrous Na_2SO_4. The solvent was evaporated off *in vacuo*, and recrystallization of the residue from AcOEt afforded 7.0 g (48%) of colorless prisms: mp 115—117 °C. IR ν_{max}^{Nujol} cm^{-1}: 2230, 1660, 1615, 1320, 1260, 1170, 1160, 1110, 835, 785. NMR ($CDCl_3$) δ: 2.23 (6H, s), 7.47 (1H, d, J=9 Hz), 8.07 (1H, dd, J=2, 9 Hz), 8.22 (1H, d, J=2 Hz), 8.37 (1H, s).

6-(1-Hydroxy-1-methylethyl)-4-oxo-4*H*-1-benzopyran-3-carbonitrile (8) and 6-Isopropenyl-4-oxo-4*H*-1-benzopyran-3-carbonitrile (11)——a) A mixture of **10** (2.0 g, 6.84 mmol), AcOH (20 ml), and H_2O (5 ml) was heated at 100 °C for 1 h and the reaction mixture was concentrated *in vacuo*. The residue was chromatographed on a column of silica gel (100 g) and eluted with $CHCl_3$–Me_2CO–HCO_2H (20 : 1 : 0.1). The compound eluted first was recrystallized from EtOH, affording 600 mg (42%) of colorless prisms, **11**: mp 142—144 °C. *Anal.* Calcd for $C_{13}H_9NO_2$: C, 73.92; H, 4.30; N, 6.63. Found: C, 74.05; H, 4.37; N, 6.64. IR ν_{max}^{Nujol} cm^{-1}: 2230, 1665, 1605, 1320, 1165, 850, 780. NMR ($CDCl_3$) δ: 2.27 (3H, br s), 5.33 (1H, m), 5.60 (1H, br s), 7.63 (1H, d, J=9 Hz), 8.07 (1H, dd, J=2, 9 Hz), 8.35 (1H, d, J=2 Hz), 8.57 (1H, s). The compound eluted second was recrystallized from EtOH, giving 190 mg (12%) of colorless plates, **8**: mp 166—167 °C. *Anal.* Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.11; H, 4.85; N, 5.99. IR ν_{max}^{Nujol} cm^{-1}: 3500, 3360, 2230, 1665, 1615, 1320, 1180, 830, 780. NMR ($CDCl_3$) δ: 1.48 (6H, s), 5.20 (1H, s), 7.55 (1H, d, J=8 Hz), 7.93 (1H, dd, J=2, 8 Hz), 8.15 (1H, d, J=2 Hz), 9.07 (1H, s).

b) A solution of **10** (9.6 g, 33 mmol) in 1 N NaOH (250 ml) was stirred for 2 h at room temperature and acidified with dil. HCl. The precipitate was extracted with AcOEt (200 ml × 3) and the AcOEt layer was washed with H_2O (200 ml × 2) and sat. aqueous NaCl (200 ml), dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed on a column of silica gel (200 g) and eluted with $CHCl_3$–Me_2CO–HCO_2H (9 : 1 : 0.1). The compound eluted first was recrystallized from EtOH, giving 1.5 g (18%) of colorless crystals, **11**. The compound eluted second was recrystallized from EtOH and afforded 4.36 g (58%) of colorless crystals, **8**.

6-Isopropenyl-4-oxo-4*H*-1-benzopyran-3-carbonitrile (11) and 6-(1-Acetoxy-1-methylethyl)-4-oxo-4*H*-1-benzopyran-3-carbonitrile (13)——A mixture of **10** (2.0 g, 6.85 mmol), AcONa (575 mg), and *N*,*N*-dimethylformamide (DMF) (20 ml) was heated at 60 °C for 1 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was chromatographed on a column of silica gel (100 g) and eluted with $CHCl_3$–Me_2CO–HCO_2H (20 : 1 : 0.1). The compound eluted first was recrystallized from EtOH, giving 1.07 g (85%) of colorless prisms, **11**. The compound eluted second was recrystallized from EtOH, affording 90 mg (5%) of colorless needles, **13**: mp 164—168 °C. *Anal.* Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.35; H, 4.83; N, 5.16. IR ν_{max}^{Nujol} cm^{-1}: 2230, 1720, 1660, 1615, 1320, 1250, 1170, 847. NMR ($CDCl_3$) δ: 1.82 (6H, s), 2.07 (3H, s), 7.57 (1H, d, J=8 Hz), 7.88 (1H, dd, J=2, 8 Hz), 8.27 (1H, d, J=2 Hz), 8.47 (1H, s).

Ethyl 2-Amino-7-(1-hydroxy-1-methylethyl)-5-oxo-5*H*-[1]-benzopyrano[2,3-*b*]pyridine-3-carboxylate (6)——a) A mixture of **8** (4.7 g, 20.5 mmol), EtOH (100 ml), piperidine (1.9 g, 22.4 mmol), and ethyl cyanoacetate (2.5 g, 22.1 mmol) was refluxed for 3 h. After the reaction mixture had been cooled with ice, the precipitated crystals were collected by filtration. The crystals were chromatographed on a column of silica gel (120 g) and eluted with $CHCl_3$–Me_2CO–HCO_2H (9 : 1 : 0.1). The eluate was concentrated and EtOH was added to the residue. The insoluble material was collected by filtration and recrystallized from $CHCl_3$, giving 4.86 g (69%) of colorless needles: mp 263—264 °C (dec.). *Anal.* Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 62.97; H, 5.14; N, 8.09. IR ν_{max}^{Nujol} cm^{-1}:

3400, 3150, 1690, 1615, 1575, 1285, 1230, 1125, 790. NMR (DMSO-d_6) δ: 1.40 (3H, t, J=7 Hz), 1.52 (6H, s), 4.37 (2H, q, J=7 Hz), 5.00 (1H, mound), 7.50 (1H, d, J=9 Hz), 7.95 (1H, dd, J=2, 9 Hz), 8.17 (2H, mound), 8.23 (1H, d, J=2 Hz), 8.80 (1H, s).

b) A mixture of ethyl 2-amino-7-isopropyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carboxylate (**7**, 326 mg, 1.0 mmol), NBS (190 mg, 1.06 mmol), benzoylperoxide (20 mg, 8 mol%), CCl_4 (30 ml), and H_2O (0.2 ml) was refluxed for 15 min and then cooled. The precipitate was collected by filtration and chromatographed on a column of silica gel (25 g), which was eluted with $CHCl_3$–Me_2CO–HCO_2H (9 : 1 : 0.1). The eluate was concentrated and EtOH was added to the residue. The insoluble material, collected by filtration, gave 54 mg (16%) of colorless crystals: mp 263—264 °C.

2-Amino-7-(1-hydroxy-1-methylethyl)-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carboxylic Acid (2)——A mixture of **6** (4.8 g, 14 mmol), 0.5 N NaOH (80 ml), and EtOH (300 ml) was stirred for 2 h at 50 °C, then the solvent was evaporated off. H_2O (300 ml) and AcOEt (100 ml) were added to the residue. The water layer was separated and acidified with 10% HCl, and the precipitate was collected by centrifugation (5000 rpm, 10 min). H_2O (100 ml) was added to the precipitate and the mixture was stirred well and centrifuged (8000 rpm, 10 min). This treatment was repeated once more and the precipitate obtained was recrystallized from DMF–EtOH–H_2O, affording 3.83 g (87%) of colorless crystals: mp (undefined) *Anal.* Calcd for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91. Found: C, 60.76; H, 4.37; N, 9.20. IR ν_{max}^{Nujol} cm^{-1}: 3450, 3320, 1680, 1665, 1610, 1535, 1230, 1220, 1160, 1120, 830, 790. NMR (DMSO-d_6) δ: 1.53 (6H, s), 5.12 (1H, mound), 7.50 (1H, d, J=9 Hz), 7.92 (1H, dd, J=2, 9 Hz), 8.20 (1H, d, J=2 Hz), 8.20 (2H, mound), 8.85 (1H, s), 13.38 (1H, mound).

2-Amino-7-(1-hydroxy-1-methylethyl)-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carboxylic Acid (2) and 7-Acetyl-2-amino-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carboxylic Acid (4)——Oxygen gas was bubbled into a solution of **1** (1.49 g, 5 mmol) in 0.1 N NaOH (100 ml) at 70 °C under IR irradiation overnight. The reaction mixture was acidified with 1 N HCl and the precipitate was collected by filtration, washed with H_2O and dried *in vacuo*. One-tenth of this precipitate was chromatographed on a column of silica gel (10 g) which was eluted with $CHCl_3$–Me_2CO–HCO_2H (9 : 1 : 0.1). The first eluate was concentrated to dryness *in vacuo*, giving 51 mg (34%) of colorless crystals. Its NMR spectrum was identical with that of **4** (see below). The second eluate was concentrated to dryness *in vacuo*, affording 57 mg (36%) of colorless crystals. Its NMR spectrum was identical with that of **2**.

6-Isopropenyl-2,3-epoxy-4-oxo-4*H*-1-benzopyran-3-carbonitrile (14)——A mixture of **11** (200 mg, 0.95 mmol), $NaHCO_3$ (100 mg), 40% CH_3CO_3H (0.1 ml), and $CHCl_3$ (5 ml) was stirred for 30 min at room temperature, and excess aqueous $Na_2S_2O_4$ was added to the reaction mixture. The $CHCl_3$ layer was dried over anhydrous Na_2SO_4 and concentrated to dryness *in vacuo*. The residue was chromatographed on a column of silica gel (20 g) and eluted with $CHCl_3$. The eulate was concentrated *in vacuo*, giving 160 mg (74%) of colorless crystals: mp 105—107 °C. *Anal.* Calcd for $C_{13}H_9NO_3 \cdot 0.1H_2O$: C, 68.18; H, 4.05; N, 6.12. Found: C, 68.11; H, 4.05; N, 6.13. IR ν_{max}^{Nujol} cm^{-1}: 1695, 1605, 1290, 1210, 1140, 1115, 1100, 900, 785. NMR ($CDCl_3$) δ: 2.13 (3H, m), 5.17 (1H, m), 5.40 (1H, m), 6.07 (1H, s), 7.08 (1H, d, J=9 Hz), 7.78 (1H, dd, J=2, 9 Hz), 7.93 (1H, d, J=2 Hz). MS *m/e*: 227 (M^+), 211, 199, 173.

Ethyl 2-Amino-7-isopropenyl-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carboxylate (15)——A mixture of **11** (800 mg, 3.79 mmol), EtOH (40 ml), piperidine (0.6 ml), and ethyl cyanoacetate (0.7 ml) was refluxed for 3 h. The reaction mixture was allowed to stand overnight at room temperature, and the precipitated crystals were collected by filtration and washed with EtOH, giving 1.09 g (89%) of colorless crystals: mp 227—230 °C (dec.). *Anal.* Calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.28; H, 4.81; N, 8.37. IR ν_{max}^{Nujol} cm^{-1}: 3400, 3270, 3170, 1710, 1640, 1290, 1280, 1240, 835, 790. NMR (CF_3CO_2D) δ: 1.53 (3H, t, J=7 Hz), 2.23 (3H, br s), 4.53 (2H, q, J=7 Hz), 5.30 (1H, br s), 5.50 (1H, br s), 7.53 (1H, d, J=9 Hz), 8.03 (1H, dd, J=2, 9 Hz), 8.26 (1H, d, J=2 Hz), 9.34 (1H, s).

Ethyl 2-Amino-7-(1,2-epoxy-1-methylethyl)-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carboxylate (12) and Ethyl 7-Acetyl-2-amino-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carboxylate (16)——A mixture of **15** (400 mg, 1.23 mmol), *m*-chloroperbenzoic acid (340 mg, 1.96 mmol), and $CHCl_3$ (20 ml) was refluxed for 1 h. The reaction mixture was washed successively with water, 10% $Na_2S_2O_4$ solution, and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on a column of silica gel (50 g) and eluted with $CHCl_3$–Me_2CO–HCO_2H (20 : 1 : 0.1). The first eluate was concentrated to dryness *in vacuo* and the residue was recrystallized from $CHCl_3$, giving 230 mg (55%) of colorless crystals of **12**: mp (undefined) *Anal.* Calcd for $C_{18}H_{16}N_2O_5 \cdot 0.3H_2O$: C, 62.53; H, 4.74; N, 8.10. Found: C, 62.13; H, 4.47; N, 8.11. IR ν_{max}^{Nujol} cm^{-1}: 3380, 3260, 3170, 1700, 1665, 1630, 1585, 1280, 1270, 1245, 835, 790. NMR ($CDCl_3$) δ: 1.41 (3H, t, J=7 Hz), 1.79 (3H, s), 2.83 (1H, d, J=5 Hz), 3.03 (1H, d, J=5 Hz), 4.40 (2H, q, J=7 Hz), 5.95 (1H, mound), 7.45 (1H, d, J=9 Hz), 7.70 (1H, dd, J=2, 9 Hz), 8.27 (1H, d, J=2 Hz), 8.35 (1H, mound), 9.14 (1H, s). The second eluate was concentrated to dryness *in vacuo* and residue was rechromatographed on a column of silica gel (8 g), which was eluted with $CHCl_3$–Me_2CO–HCO_2H (20 : 1 : 0.1). The eluate was concentrated *in vacuo*, giving 25 mg (6.2%) of colorless crystals. The NMR spectrum was identical with that of **16** (see below).

Ethyl 2-Amino-7-(2-hydroxy-1-methylethyl)-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carboxylate (17)——A mixture of **12** (800 mg, 2.35 mmol), 5% Pd–C (700 mg), EtOH (50 ml), and tetrahydrofuran (THF) (150 ml) was hydrogenated under atmospheric pressure at room temperature over a 2-h period, then the catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was chromatographed on a column of silica gel (80 g), eluted with $CHCl_3$–Me_2CO–HCO_2H (9 : 1 : 0.1). The eluate was concentrated to dryness *in vacuo* and the residue was

recrystallized from $CHCl_3$, affording 499 mg (61%) of colorless prisms: mp 255—256 °C. *Anal.* Calcd for $C_{18}H_{18}N_2O_5 \cdot 0.5H_2O$: C, 61.35; H, 5.43; N, 7.95. Found: C, 61.51; H, 5.14; N, 7.67. IR ν_{max}^{Nujol} cm^{-1}: 3500, 3410, 3360, 3160, 1690, 1680, 1620, 1290, 1270, 1230, 790. NMR (DMSO-d_6) δ: 1.28 (3H, d, J=7 Hz), 1.38 (3H, t, J=7 Hz), 3.00 (1H, sextet, J=7 Hz), 3.60 (2H, d, J=7 Hz), 4.33 (1H, mound), 4.38 (2H, q, J=7 Hz), 7.50 (1H, d, J=8 Hz), 7.77 (1H, dd, J=2, 8 Hz), 7.98 (1H, d, J=2 Hz), 8.22 (2H, br s), 8.82 (1H, s).

2-Amino-7-(2-hydroxy-1-methylethyl)-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carboxylic Acid (3)——A mixture of **17** (480 mg, 1.37 mmol), EtOH (40 ml), H_2O (5 ml), and 1 N NaOH (5 ml) was stirred for 80 min at 50 °C, and the reaction mixture was concentrated *in vacuo*. The residue was dissolved in water and acidified with 10% HCl. The precipitate was collected by filtration, washed with water and recrystallized from DMF–EtOH–H_2O, giving 386 mg (90%) of colorless crystals of **3**: mp >300 °C. *Anal.* Calcd for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91. Found: C, 61.11; H, 4.31; N, 8.70. IR ν_{max}^{Nujol} cm^{-1}: 3470, 3350, 1680, 1665, 1580, 1270, 1230, 1015, 825, 800, 790. NMR (DMSO-d_6) δ: 1.28 (3H, d, J=7 Hz), 3.03 (1H, sextet, J=7 Hz), 3.60 (2H, d, J=7 Hz), 4.50 (1H, mound), 7.50 (1H, d, J=8 Hz), 7.73 (1H, dd, J=2, 8 Hz), 7.98 (1H, d, J=2 Hz), 8.27 (2H, br s), 8.90 (1H, s), 13.33 (1H, mound).

Ethyl 7-Acetyl-2-amino-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carboxylate (16)——A mixture of **18**[7] (400 mg, 1.88 mmol), EtOH (10 ml), piperidine (0.3 ml), and ethyl cyanoacetate (0.3 ml) was refluxed for 1.5 h, then allowed to cool. The precipitated crystals were collected by filtration, washed with EtOH, and dried *in vacuo*, giving 590 mg (96%) of colorless needles of **16**: mp >300 °C. *Anal.* Calcd for $C_{17}H_{14}N_2O_5$: C, 62.57; H, 4.32; N, 8.59. Found: C, 62.59; H, 4.24; N, 8.43. IR ν_{max}^{Nujol} cm^{-1}: 3370, 3250, 1690, 1665, 1630, 1620, 1600, 1595, 1290, 1260, 1235, 1125, 1020, 840, 805, 790. NMR (CF_3CO_2D) δ: 1.57 (3H, t, J=7 Hz), 2.92 (3H, s), 4.67 (2H, q, J=7 Hz), 7.92 (1H, d, J=9 Hz), 8.72 (1H, dd, J=2, 9 Hz), 9.17 (1H, d, J=2 Hz), 9.57 (1H, s).

7-Acetyl-2-amino-5-oxo-5*H*-[1]benzopyrano[2,3-*b*]pyridine-3-carboxylic Acid (4)——A mixture of **16** (590 mg, 1.81 mmol), EtOH (40 ml), H_2O (6 ml), and 1 N NaOH (6 ml) was stirred for 2 h at 50 °C, and the reaction mixture was concentrated *in vacuo*. The residue was dissolved in hot water (500 ml), and insoluble material was removed by filtration. The filtrate was acidified with 10% HCl and the precipitate was collected by filtration, washed with H_2O and recrystallized from DMF–EtOH–H_2O, affording 286 mg (53%) of colorless prisms of **4**: mp >300 °C. *Anal.* Calcd for $C_{15}H_{10}N_2O_5$: C, 60.40; H, 3.38; N, 9.39. Found: C, 60.23; H, 3.41; N, 9.38. IR ν_{max}^{Nujol} cm^{-1}: 3350, 3150, 3090, 1710, 1685, 1630, 1620, 1590, 1250, 1210, 830, 795, 785. NMR (CF_3CO_2D) δ: 2.93 (3H, s), 7.92 (1H, d, J=9 Hz), 8.72 (1H, dd, J=2, 9 Hz), 9.15 (1H, d, J=2 Hz), 9.63 (1H, s).

2-Amino-6-hydroxy-5-(2-hydroxy-5-isopropylbenzoyl)pyridine-3-carboxylic Acid (5)——A solution of **1** (29.8 g, 0.10 mol) in 2 N NaOH (500 ml) was refluxed for 2.5 h. After the reaction mixture had been cooled with ice, it was acidified with conc. HCl (100 ml). The yellow crystals which had precipitated were collected by filtration, washed H_2O and recrystallized three times from DMF–H_2O, affording 22.63 g (72%) of **5** as yellow needles: mp 239—241 °C (dec.). *Anal.* Calcd for $C_{16}H_{16}N_2O_5$: C, 60.76; H, 5.10; N, 8.86. Found: C, 60.85; H, 5.10; N, 8.88. IR ν_{max}^{KBr} cm^{-1}: 3390, 3220, 1685, 1620, 1260—1240. NMR (DMSO-d_6) δ: 1.18 (6H, d, J=6 Hz), 2.82 (1H, quintet, J=6 Hz), 6.82 (1H, d, J=9 Hz), 7.29 (1H, dd, J=2, 9 Hz), 7.59 (1H, d, J=2 Hz), *ca.* 7.7 (2H, br s), 8.20 (1H, s), 10.98 (1H, br s), 11.35 (1H, mound).

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