Studies on Antibacterial Agents. II.[1] Synthesis and Antibacterial Activities of Substituted 1,2-Dihydro-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylic Acids

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A series of substituted 1,2-dihydro-6-oxo-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylic acids for the treatment of systemic infections was synthesized *via* 7-bromo-3-ethylthio-4,5-difluoro-2-methylindole (3), which was prepared by Gassman's indole synthesis in excellent yield. The synthesized pyrroloquinolines were tested for their antibacterial activities. 8-Fluoro-1,2-dihydro-2-methyl-9-(4-methyl-1-piperazinyl)-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylic acid showed a potent antibacterial activity against gram-positive and gram-negative bacteria.

Keywords pyrrolo[3,2,1-*ij*]quinoline; quinolone carboxylic acid; indole; *Pseudomonas aeruginosa*; antibacterial activity; systemic infection

Among synthetic antibacterial agents, a number of investigators have recently focused on the research and development of quinolone carboxylic acid derivatives, some of which are now on the market.

We have been searching for compounds with more potent and broad-spectrum antibacterial activity for the treatment of systemic infections. In a previous paper,[1] we reported the synthesis and antibacterial activity of tricyclic benzo-[*i,j*]quinolizine derivatives in consideration of the substitution effect of the 1- and 8-positions of quinoline ring. Among them, 9-fluoro-6,7-dihydro-5-methyl-8-(4-methyl-1-piperazinyl)-1-oxo-1*H*,5*H*-benzo[*i,j*]quinolizine-2-carboxylic acid (OPC-7241) and 9-fluoro-6,7-dihydro-8-(4-hydroxy-1-piperidyl)-1-oxo-1*H*,5*H*-benzo[*i,j*]quinolizine-2-carboxylic acid (OPC-7251) exhibited potent antibacterial activity against gram-positive and gram-negative bacterias. With much interest in the activity of the tricyclic quinolone analogues, we synthesized pyrrolo[3,2,1-*ij*]quinoline carboxylic acids (Fig. 1).

We wish to report here the synthesis and antibacterial activities of variously substituted 1,2-hydro-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylic acid derivatives.

Synthesis

Parikh *et al.*[2] reported a new synthesis of 8,9-difluoropyrroloquinoline carboxylic acid derivative (**6**) from 2,3,4-trifluoronitrobenzene. However, their method has a disadvantage for industrial-scale synthesis, because overall yield is unsatisfactory (16%) and some of the intermediates are purified by use of silica gel column chromatography. We accomplished the synthesis of **6** in 49% overall yield from commercially available 3,4-difluoroaniline (**1**) without purification by silica gel column chromatography. Namely,

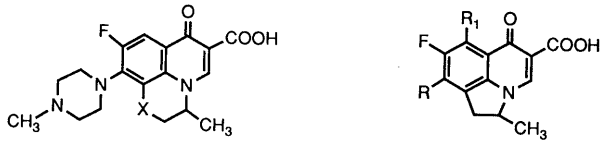


Fig. 1

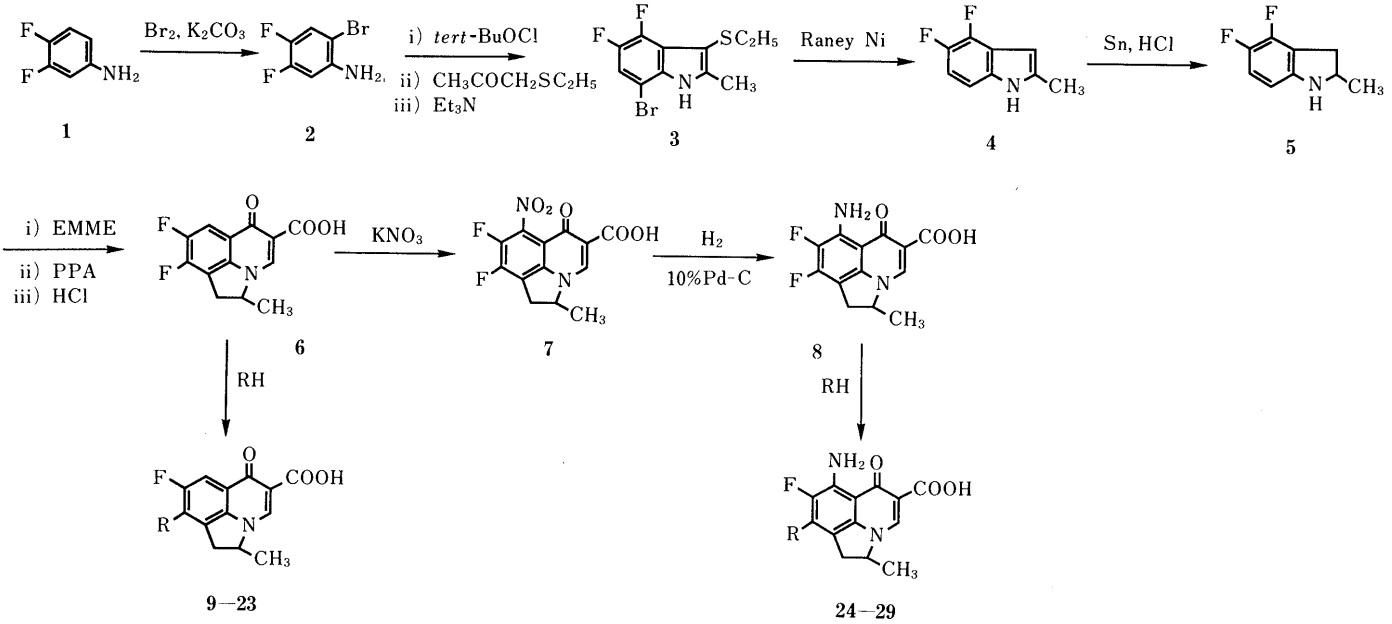
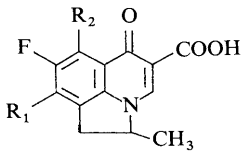
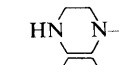
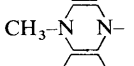
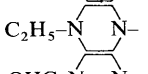
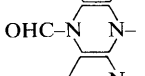
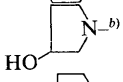
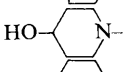
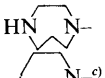
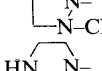
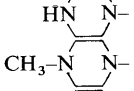
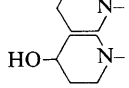


Chart 1

TABLE I. Substituted 1,2-Dihydro-6-oxopyrrolo[3,2,1-*ij*]quinoline-5-carboxylic Acids



Compd. No.	R_1	R_2	Recryst. solvent	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
9		H	DMF	53	235—236	$C_{17}H_{18}FN_3O_3 \cdot 2H_2O$	55.58 (55.40)	6.04 6.11	11.44 11.43)
10		H	DMF	78	242—244	$C_{18}H_{20}FN_3O_3$	62.60 (62.36)	5.84 5.84	12.17 12.10)
11		H	EtOH	75	248—250	$C_{19}H_{22}FN_3O_3$	63.50 (63.43)	6.17 6.06	11.69 11.86)
12		H	DMF	86[a]	>300	$C_{18}H_{18}FN_3O_4 \cdot 1/2H_2O$	58.69 (58.75)	5.20 4.90	11.41 11.46)
13		H	DMF	80	>300	$C_{17}H_{17}FN_2O_3$	64.55 (64.28)	5.42 5.57	8.86 8.72)
14		H	DMF	67	>300	$C_{17}H_{17}FN_2O_4$	61.44 (61.16)	5.16 4.93	8.43 8.52)
15		H	EtOH	63	239—242 (dec.)	$C_{18}H_{19}FN_2O_3$	65.44 (65.44)	5.80 5.60	8.48 8.56)
16		H	EtOH–H_2O	67	228—231	$C_{18}H_{19}FN_2O_4$	62.42 (62.25)	5.53 5.67	8.09 7.92)
17		H	DMF	78	277—280	$C_{17}H_{17}FN_2O_4$	61.44 (61.23)	5.16 5.29	8.43 8.32)
18		H	DMF	74	>300	$C_{17}H_{17}FN_2O_3S$	58.61 (58.52)	4.92 5.11	8.04 7.92)
19		H	EtOH–H_2O	55	262—265 (dec.)	$C_{18}H_{20}FN_3O_3 \cdot 2H_2O$	56.68 (56.36)	6.34 6.31	11.02 10.88)
20		H	DMF	72	278—280 (dec.)	$C_{17}H_{18}FN_3O_3$	61.62 (61.18)	5.48 5.47	12.68 12.81)
21		H	DMF	73	292—295 (dec.)	$C_{16}H_{16}FN_3O_3$	60.56 (60.65)	5.08 4.93	13.24 13.29)
22		H	DMF–EtOH	90[d]	238—240 (dec.)	$C_{18}H_{20}FN_3O_3$	62.60 (62.55)	5.84 5.81	12.17 12.24)
23		H	DMF–EtOH	63[e]	267—268	$C_{17}H_{18}FN_3O_3$	61.62 (61.32)	5.48 5.44	12.68 12.84)
24		NH_2	DMF	75	256—259 (dec.)	$C_{17}H_{19}FN_4O_3 \cdot H_2O$	56.04 (55.94)	5.81 5.88	15.38 15.24)
25		NH_2	DMF–EtOH	82	240—243 (dec.)	$C_{18}H_{21}FN_4O_3$	59.99 (59.76)	5.87 5.86	15.55 15.76)
26		NH_2	DMF–EtOH	62	273—276 (dec.)	$C_{18}H_{20}FN_3O_3$	62.60 (62.71)	5.84 5.88	12.17 12.20)
27		NH_2	DMF	58	287—292 (dec.)	$C_{18}H_{21}FN_3O_4$	59.66 (59.67)	5.84 5.58	11.60 11.71)
28		NH_2	DMF	73	296—299 (dec.)	$C_{17}H_{18}FN_3O_3$	61.62 (61.78)	5.48 5.50	12.68 12.54)
29		NH_2	DMF	51	>300	$C_{17}H_{18}FN_3O_4$	58.79 (58,62)	5.22 5.20	12.10 12.36)

a) Yield from **9**. *b*) Compound **14** is a mixture of diastereomers. *c*) Ref. 7. *d*) Yield from **20**. *e*) Yield from **21**.

compound (**1**) was selectively monobrominated in CH_2Cl_2 in the presence of K_2CO_3 at $-15\,°C$ to afford 2-bromo-4,5-difluoroaniline (**2**). Fischer's indole cyclization[3] of **2** gave **3** in poor yield. Then, we investigated Gassman's indole synthesis.[4] Compound (**2**) was treated with *tert*-butyl hypochlorite at $-50\,°C$ in CH_2Cl_2, followed by the addition of ethylthio-2-propanone and treatment with triethylamino to produce **3** in excellent yield. Reductive elimination of bromine and ethylthio groups of **3** with Raney nickel gave 4,5-difluoro-2-methylindole (**4**) in 86% yield. Hydrogenation of the 2-and 3-position of **4** with tin in acetic acid gave 4,5-difluoro-2-methylindoline (**5**).

Compound (**6**) was synthesized from **5** in one pot serial operation as follows: condensation of **5** with ethoxymethylenemalonate (EMME) afforded enaminoester compounds, which was cyclized with polyphosphoric acid (PPA) and then hydrolyzed with dil. HCl. Nitration of **6** with potassium nitrate (KNO_3), followed by hydrogenation

Table II. *In Vitro* Antibacterial Activity (Minimum Inhibitory Concentration, μg/ml)

Compd. No.	*S. aureus* 209p	*S. pyogenes* IID S-23	*E. coli* NIHJ JC-2	*Ps. aeruginosa* ATCC 10145
9	1.56	3.13	0.1	0.78
10	0.39	3.13	0.05	1.56
11	0.2	1.56	0.1	3.13
12	0.78	3.13	0.39	6.25
13	0.05	1.56	0.2	1.56
14	0.39	3.13	0.39	3.13
15	0.2	1.56	0.78	3.13
16	0.2	3.13	0.39	3.13
17	0.1	1.56	0.2	1.56
18	0.1	1.56	0.2	1.56
19	3.13	6.25	0.39	3.13
20	0.39	12.5	0.78	25
21	0.2	6.25	0.39	6.25
22	1.56	50	12.5	100
23	0.2	3.13	0.78	6.25
24	0.39	3.13	0.1	0.39
25	0.2	3.13	0.05	0.78
26	0.39	25	0.78	12.5
27	0.2	6.25	0.39	6.25
28	0.39	6.25	0.78	6.25
29	0.2	12.5	0.2	3.13
OPC-7241	0.2	3.13	0.2	3.13
OFLX	0.2	1.56	0.1	1.56

of the product (**7**) with 10% palladium on carbon (10% Pd–C) provided the 7-amino compound (**8**). Finally, the acids (**6** and **8**) were allowed to react with various cyclic amines in *N*-methyl-2-pyrrolidinone (NMP) to afford the desired 9-amino derivatives (**9**—**29**) (Table I).

Biological Results

Compounds (**9**—**29**) were tested for *in vitro* antibacterial activities against gram-positive (*Staphylococcus aureus* 209p and *Streptococcus pyogenes* IID S-23) and gram-negative bacteria (*Escherichia coli* NIHJ JC-2 and *Pseudomonas aeruginosa* ATCC 10145) by serial dilution method.[5] The results are summarized in Table II. The antibacterial activities of OPC-7241[1] and ofloxacin (OFLX)[6] are also presented.

Pyrroloquinoline derivative (**10**) showed more potent activity against gram-negative bacteria, including *Ps. aeruginosa* than the corresponding benzo[*i,j*]quinolizine derivative (OPC-7241), and had the activity similar to that of pyrido[1,2,3-*de*][1,4]benzoxazine derivative (OFLX). Substitution of the hydrogen of the piperazinyl group (**9** and **24**) by a methyl group (**10** and **25**) increased the activity against *S. aureus*, but it caused a decrease in the activity against *Ps. aeruginosa*. The replacement of the piperazine side chain (**9**) by piperidazine (**20**) and pyrazolidine (**21**) side chain decreased the activity against gram-negative bacteria. Compounds (**24** and **25**) with an amino group at the 7-position on the pyrroloquinone skeleton exhibited more potent antibacterial activity against *S. aureus* and *Ps. aeruginosa* than did unsubstituted compounds (**9** and **10**). Among all of the above compounds, compound (**10**) showed a potent, broad-spectrum activity and a good pharmacokinetic profile.

Experimental

All the melting points are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM-390 or Bruker AC-200 NMR spectrometer using tetramethylsilane as an internal standard.

2-Bromo-4,5-difluoroaniline (2) A solution of bromine (16.0 g, 0.1 mol) in CH_2Cl_2 (160 ml) was added dropwise into a suspension of 3,4-difluoroaniline (**1**) (12.9 g, 0.1 mol) and K_2CO_3 (13.8 g, 0.1 mol) in CH_2Cl_2 (260 ml) at −15 °C. After the addition, the mixture was stirred at the same temperature for 30 min. The reaction mixture was poured into ice-water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over $MgSO_4$ and concentrated. The residue was distilled to give **2** (17.7 g, 85%), bp 90—93 °C (1 mmHg). NMR ($CDCl_3$) δ: 3.84 (2H, br s), 6.56 (1H, dd, J=7.7, 9.4 Hz), 7.14 (1H, dd, J=6.2, 10.0 Hz). *Anal.* Calcd for $C_6H_4BrF_2N$: C, 34.63; H, 1.94; N, 6.73. Found: C, 34.43; H, 1.88; N, 6.65.

7-Bromo-3-ethylthio-4,5-diflouoro-2-methylindole (3) A solution of *tert*-butyl hypochlorite (60 g, 0.55 mol) was added dropwise to a vigorously stirred solution of **2** (115 g, 0.55 mol) in CH_2Cl_2 (1 l). After 5—10 min, a solution of ethylthio-2-propanone (65.6 g, 0.55 mol) in CH_2Cl_2 (100 ml) was added causing an exotherm reaction, and stirring was continued at −50 °C for 2 h. Subsequently, triethylamine (58 g, 0.57 mol) was added dropwise. After the addition, the cooling bath was removed and the solution was allowed to warm to room temperature. Water (1 l) was added and the organic layer was separated, dried over $MgSO_4$ and concentrated. The residue was recrystallized from hexane to give **3** (158 g, 93%) as colorless needles, mp 65—66 °C. NMR ($CDCl_3$) δ: 1.17 (3H, t, J=7.3 Hz), 2.54 (3H, s), 2.73 (2H, q, J=7.3 Hz), 7.16 (1H, q, J=6.4, 9.9 Hz), 8.20 (1H, br s); *Anal.* Calcd for $C_{11}H_{10}BrF_2NS$: C, 43.15; H, 3.29; N, 4.57. Found: C, 43.08; H, 3.18; N, 4.57.

4,5-Difluoro-2-methylindole (4) Activated Raney nickel (w-2) (1.5 kg) was added to a solution of **3** (174 g, 0.6 mol) in EtOH (3 l) and the mixture was heated under reflux for 3 h. The catalyst was filtered off, and the filtrate was concentrated *in vacuo*. The residue was recrystallized from *n*-hexane to give **4** (85.5 g, 86%) as pale yellow prisms, mp 72—74 °C. NMR ($CDCl_3$) δ: 2.43 (3H, s), 6.31 (1H, br s), 6.08—7.00 (2H, m), 7.89 (1H, br s); *Anal.* Calcd for $C_9H_7F_2N$: C, 64.67; H, 4.22; N, 8.38. Found: C, 64.60; H, 4.09; N, 8.37.

4,5-Difluoro-2-methylindoline (5) Concentrated HCl (1.5 l) was added to a mixture of **4** (93 g, 0.57 mol) and tin (200 g, 1.7 g atom) in AcOH (1.5 l) under reflux during 1 h. After heating was continued for 2 h, the mixture was concentrated *in vacuo*, and the residue was basified with 10% NaOH and extracted with ether. The ether solution was washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was distilled to give **5** (80 g, 85%), bp 90 °C (4 mmHg). NMR ($CDCl_3$) δ: 1.29 (3H, d, J=6.2 Hz), 2.66 (1H, dd, J=7.6, 15.8 Hz), 3.21 (1H, dd, J=7.6, 15.8 Hz), 3.60 (1H, br s), 3.90—4.17 (1H, m), 6.24 (1H, dd, J=3.2, 8.4 Hz), 6.78 (1H, m); *Anal.* Calcd for $C_9H_9F_2N$; C, 63.90; H, 5.38; N, 8.28. Found: C, 63.88; H, 5.36; N, 8.16.

8,9-Difluoro-1,2-dihydro-2-methyl-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylic Acid (6) A mixture of **5** (33.8 g, 0.2 mol) and EMME (65.4 g, 0.3 mol) was heated at 150 °C for 2 h. PPA (101 g, 0.3 mol) was added to the oily mixture at 120—130 °C and then heated at the same temperature for 2 h. A mixture of concentrated HCl (35 ml), water (170 ml) and EtOH (500 ml) was added to the reaction mixture and heated under reflux for 2 h. After cooling, water was added to the mixture and the resulting precipitates were collected by filtration. Recrystallization from *N,N*-dimethylformamide (DMF) gave **6** (45.1 g, 85%) as colorless prisms, mp 296—297 °C. NMR ($CDCl_3$) δ: 1.67 (3H, d, J=6.5 Hz), 3.30 (1H, dd, J=8.3, 17.2 Hz), 3.90 (1H, J=8.3, 17.2 Hz), 5.12—5.34 (1H, m), 7.97 (1H, dd, J=7.2, 10.6 Hz), 9.17 (1H, s). *Anal.* Calcd for $C_{13}H_9F_2NO_3$; C, 58.87; H, 3.42; N, 5.28. Found: C, 58.92, H, 3.42; N, 5.33.

8,9-Difluoro-1,2-dihydro-2-methyl-7-nitro-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]-quinoline-5-carboxylic Acid (7) KNO_3 (17.0 g, 0.17 mol) was added to a solution of **6** (11.5 g, 43 mmol) in concentrated H_2SO_4 (120 ml). The mixture was heated at 70 °C for 2 h. After cooling, the reaction mixture was poured into ice-water and the resulting precipitates were collected by filtration. Recrystallization from DMF gave **7** (6.8 g, 51%) as white powder, mp 265—268 °C (dec.). NMR (DMSO-d_6) δ: 1.65 (3H, d, J=6.6 Hz), 3.33 (1H, dd, J=4.6, 18.0 Hz), 3.92 (1H, dd, J=8.6, 18.0 Hz), 5.04–5.38 (1H, m), 9.26 (1H, s), 14.3 (1H, br s). *Anal.* Calcd for $C_{13}H_8F_2N_2O_5$: C, 50.33; H, 2.60; N, 9.03. Found: C, 50.21; H, 2.61; N, 8.89.

7-Amino-8,9-difluoro-1,2-dihydro-2-methyl-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylic Acid (8) A mixture of **7** (6.0 g, 19 mmol) and 10% Pd–C (0.5 g) in DMF (300 ml) was stirred at room temperature under atmospheric pressure of hydrogen until the absorption of hydrogen ceased. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. EtOH was added to the residue and the precipitates were collected by filtration. Recrystallization from DMF gave **8** (2.7 g, 50%) as white pow-

der, mp 265—268 °C (dec.). NMR (DMSO-d_6) δ: 1.53 (3H, d, J=6.0 Hz), 2.96 (1H, dd, J=3.7, 16.0 Hz), 3.57 (1H, dd, J=8.1, 16.0 Hz), 4.85—5.20 (1H, m), 7.01 (2H, br s), 8.79 (1H, s), 14.82 (1H, br s). *Anal.* Calcd for $C_{13}H_{10}F_2N_2O_3$: C, 55.72; H, 3.60; N, 10.00. Found: C, 55.48; H, 3.63; N, 9.88.

8-Fluoro-1,2-dihydro-2-methyl-9-(4-methyl-1-piperazinyl)-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylic Acid (10) A mixture of **6** (2.7 g, 10 mmol) and *N*-methylpiperazine (5.0 g, 50 mmol) in NMP (30 ml) was heated at 120 °C. The reaction mixture was concentrated *in vacuo*, and then EtOH was added to the residue. The resulting precipitates were collected by filtration and recrystallized from EtOH to give **10** (2.7 g, 78%). NMR ($CDCl_3$) δ: 1.71 (3H, d, J=6.5 Hz), 2.39 (3H, s), 2.50—2.68 (4H, m), 3.24 (1H, dd, J=5.3, 16.6 Hz), 3.33—3.50 (4H, m), 3.89 (1H, dd, J=8.8, 16.6 Hz), 4.83—5.05 (1H, m), 7.61 (1H, d, J=12.4 Hz), 8.64 (1H, S), 15.32 (1H, br s). The melting point and elemental analysis data are given in Table I.

Compounds (**9**, **11**, **13**—**21** and **24**—**29**) were obtained by the same procedure as described for **10**; the yield, the melting point and elemental analysis data are given in Table I.

8-Fluoro-9-(4-formyl-1-piperazinyl)-1,2-dihydro-2-methyl-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylic Acid (12) A mixture of acetic anhydride (17 ml, 0.18 mol) and formic acid (12.1 ml, 0.32 mol) was heated at 50°C for 20 min, and then **9** (6.6 g, 0.02 mol) was added. The mixture was heated at 80 °C for 2 h. After cooling, the reaction mixture was poured into ether. The resulting precipitates were collected by filtration and recrystallized from DMF to give **12** (6.2 g, 86%). NMR ($CDCl_3$) δ: 1.73 (3H, d, J=6.6 Hz), 3.15—4.00 (10H, m), 4.88—5.07 (1H, m), 7.77 (1H, d, J=12.2 Hz), 8.14 (1H, s), 8.74 (1H, s), 15.17 (1H, br s). The melting point and elemental analysis data are given in Table I.

8-Fluoro-1,2-dihydro-2-methyl-9-(2-methyl-1-pyrazolidinyl)-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylic Acid (23) Amixture of **21** (0.79 g, 2.5 mmol), sodium formate (0.75 g, 11 mmol), formic acid (6 ml, 0.16 mol) and 37% formaline (6 ml, 0.08 mol)[8] was heated under reflux for 5 h. The reaction mixture was concentrated *in vacuo*, and the residue was basified with 10% NaOH and filtrated. The filtrate was adjusted to pH 7.8 with AcOH. The resulting precipitates were collected by filtration and recrystallized from DMF to give **23** (0.58 g, 63%). NMR ($CDCl_3$) δ: 1.67 (3H, d, J=6.6 Hz), 2.10—2.35 (2H, m), 2.53 (3H, s), 2.88—3.13 (2H, m), 3.37 (1H, dd, J=5.2, 17.4 Hz), 3.48—3.95 (2H, m), 4.04 (1H, dd, J=8.5, 17.4 Hz), 7.58 (1H, d, J=13.0 Hz), 8.57 (1H, s), 15.60 (1H, br s). The melting point and elemental analysis data are given in Table I.

Compound (**22**) was obtained from **20** by the same procedure as described for **23**. The yield, melting point and elemental analysis data are given in Table I.

References and Notes

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