Synthesis of Quinone Derivatives of Quinocarcin

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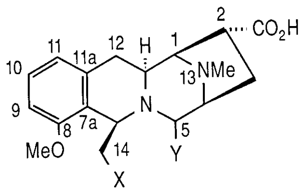
O-Demethyl-DX-52-1 (3a) was prepared from quinocarcin (1) in two steps (cyanation and O-demethylation). Upon treatment with Fremy's salt, 3a and its esters 3b, 3c afforded the desired quinone 4—6 in good yields. Various substituted quinones 12—37, 47—50 were prepared from 4—6 by Thiele acetylation followed by hydrolysis of acetates and halogenation, by direct addition of amine, alcohol and mercaptan, and by epoxidation and subsequent opening of the epoxide ring with aniline. The quinonemonoketals 39b and 40 were obtained from the corresponding methoxyphenols 7b and 38b. Addition of hydroxylamine gave the quinoneoxime 44 regiospecifically. The antitumor activity of the bis-methylthioquinone (37) among the various derivatives was the most promising.

Keywords quinocarcin; DX-52-1; quinone; bis-methylthioquinone; oxidation; addition; quinoneoxime; quinonemonoketal

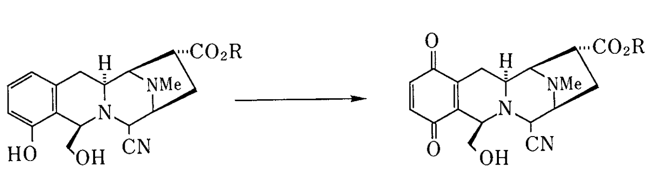
Quinocarcin (**1**),[1] isolated from the culture broths of *Streptomyces melanovinaceus*, is a novel antitumor antibiotic. In the course of our synthetic studies on quinocarcin derivatives with the aim of enhancing the antitumor activity and broadening the activity spectrum, we have reported various aromatic ring-substituted analogues in the preceeding paper.[2a)] However, except for the halogen-substituted compounds their antitumor activities did not meet our requirements. A survey of the antitumor activity of a number of polyfunctional naturally occurring compounds revealed that a quinone moiety was a common functionality in active compounds.[3)] Saframycin[4)] and naphthyridinomycin,[5)] which are structurally related to quinocarcin and also have higher antitumor potencies than quinocarcin, both contain a quinone moiety. Therefore we decided to prepare new quinone derivatives of quinocarcin in the hope of obtaining superior antitumor properties.



	X	Y
quinocarcin (**1**)	---O---	
DX-52-1 (**2**)	OH	CN

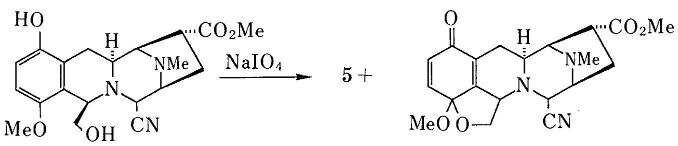
Fig. 1

Chemistry *O*-Demethyl-DX-52-1 (**3a**),[2a)] prepared readily from quinocarcin (**1**) in two steps (cyanation and demethylation), seemed to be a suitable quinone precursor. Attempts to convert **3a** and its ester **3b** into the quinones **4** and **5** met with various results. None of the desired quinone was obtained with hydrogen peroxide–ferric chloride in acetic acid, hydrogen peroxide–ruthenium(III) chloride in acetic acid or thallium(III) nitrate in methanol. Exposure of **3a** to thallium(III) trifluoroacetate in trifluoroacetic acid[6)] (TFA) generated the desired quinone **4** in rather low yield. The methyl ester **5** was also obtained in a similar manner from **3b** in slightly increased yield. In contrast, oxidation with Fremy's salt[7)] proceeded with remarkable efficiency affording the quinones **4** and **5** in good yields (Chart 1). Besides the effectiveness of Fremy's salt, the milder reaction conditions might contribute to the high yield. In the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum of **4** and **5** quinone carbons characteristically appeared at 185—188 ppm. The electron-impact mass spectrum (EIMS) of **5** showed a molecular ion peak ($m/z = 371$), while the secondary ion mass spectrum (SIMS) of **4** showed a peak of M + 3, which is expected for quinone-containing



Ph_2CN_2 → **3a** : R=H —BF_3-OEt_2 → **3b** : R=Me ← MeOH; Ph_2CN_2 → **3c** : R=$CHPh_2$

	conditions	yield
4 : R=H	$Tl(OCOCF_3)_3/CF_3CO_2H$	10%
	Fremy's salt/H_2O	65%
5 : R=Me	$Tl(OCOCF_3)_3/CF_3CO_2H$	16%
	Fremy's salt/CH_3CN-H_2O	75%
6 : R=$CHPh_2$	Fremy's salt/CH_3CN-H_2O	79%



7a **8**

Chart 1

molecules.[8)] Most of the quinone derivatives described in this report also gave a M+3 peak in SIMS. An alternative method to prepare the quinones was examined simultaneously. That is, treatment of methoxyphenol **7a**[2a)] with sodium periodate afforded the quinone **5** in 24% yield, along with the unexpected quinonemonoketal (**8**) in a small amount. The structure of **8** was established by ^{1}H, ^{13}C-NMR and mass spectrum (MS). Due to its lability to base, the methyl ester of quinone **5** could not be saponified to **4**. Therefore the acid-cleavable diphenylmethyl ester quinone (**6**) was prepared from **3c** in a similar manner.

Having established a route to the quinones **4**—**6**, we focused our attention on introduction of substituents into the quinone ring. Addition reactions toward 1,4-benzoquinone and 1,4-naphthoquinone have been described in detail.[9a)] First we examined Thiele acetylation of **4** and **5** with acetic anhydride–perchloric acid,[9b)] which gave regiospecifically the tetraacetates **9** and **10**, respectively. It was not clear why such a high specificity was obtained. The carboxylic acid **9** was transformed to the ester **11**. Exposure of **10** to potassium carbonate in methanol directly provided the 10-hydroxyquinones **12** and **13** in a ratio of 2:1. Their hydroquinones could not be isolated, even if the reaction was carried out under anaerobic conditions. The diphenylmethyl ester **11** yielded the corresponding **14** predominantly with a small amount of the 14-hydroxide. Methylation of **12** and **14** was effected with diazomethane, giving **15** and **16**. Further addition occurred with excess diazomethane to afford spirooxazolidine **18** as a mixture of stereoisomers (*ca.* 1:1) at C-11. The ester of **16** was cleaved readily with TFA to afford the corresponding carboxylic acid **17** in 77% yield, while saponification of **15** gave a complex mixture. The position of the methoxy group in **17** was determined by NMR study. That is, 11-C was coupled with 12-H (3.1 Hz), and the 7.6 Hz coupling constant between 11-C and 9-H was in agreement with three bond coupling.[10)] Halogenation of **12** and **14** was performed with bromine or *N*-chlorosuccinimide (NCS) to provide **19**—**21**, followed by methylation with CH_2N_2 to yield **22** and **23**. Subsequent ester hydrolysis of **22** provided **24** in moderate yield.

Direct addition of dimethylamine to the quinone **4** proceeded readily to give a mixture of regioisomers **25** and **26** in a ratio of *ca.* 4:3, which could be separated by preparative high-performance liquid chromatography (HPLC). Replacement of the methoxy group in **17** with dimethylamine proceeded readily to give **28**. The regiochemistry of **25** and **26** was confirmed by HPLC comparison of their acetylated analogues with **28**. Similarly the azirizinoquinone **29** was also obtained from **4** as a mixture of regioisomers. In contrast to amine, methanol addition to the quinone was very slow. The methoxyquinones **30** and **31** were obtained in 40—60% yields in 4—10 d, along with recovery of starting material (**5** or **6**). Subsequent ester cleavage of **31** afforded **32**. An attempt at ammonia addition to **4** resulted in failure, while azide added to **6** effectively, giving the aminoquinone **36** after reduction and ester cleavage. In the above addition reaction, no "bis-adduct" was obtained, while methyl mercaptan reacted with the quinone **4** to afford the bis-methylthioquinone (**37**) after oxidation with Fremy's salt. Addition of methyl mercaptan to **4** gave a complex mixture which might include compounds **a**—**d** (Chart 3), but they converged to **37** on subsequent oxidation followed by repetition of methyl mercaptan addition and oxidation.

Next we examined quinone carbon modification. Upon treatment with thallium(III) nitrate and trimethyl orthoformate, **7a** and **7b**[2a)] gave the quinonemonoketals **39a** and **39b** in moderate yields. The 10-bromo analog (**40**) was prepared similarly from **38b**. Addition of hydroxylamine and methoxylamine to the quinone **6** occurred easily to give the corresponding quinoneoximes **41** and **43** predominantly. None of the C-9 or C-10 adduct was formed, as was the case for secondary amine. Dioxime was not obtained under various reaction conditions. The regiochemistry of the oxime was confirmed by an NMR study of the corresponding acid **42**. The oxime carbon, appearing at 148.7 ppm, was coupled with 12α-H, while the quinone carbon (186.4 ppm) showed a coupling with 7-H. The regioselectivity might be due to the steric influence of the 7-hydroxymethyl substituent.

Epoxidation of **6** was effected with sodium hypochlorite,[11)] providing the epoxide **45** as a mixture of stereoisomers. 13-Nitrogen was not oxidized to N-oxide, as occurred upon treatment with *m*-chloroperbenzoic acid.[2a)] Epoxide opening of **45** with aniline[12)] gave the anilinohy-

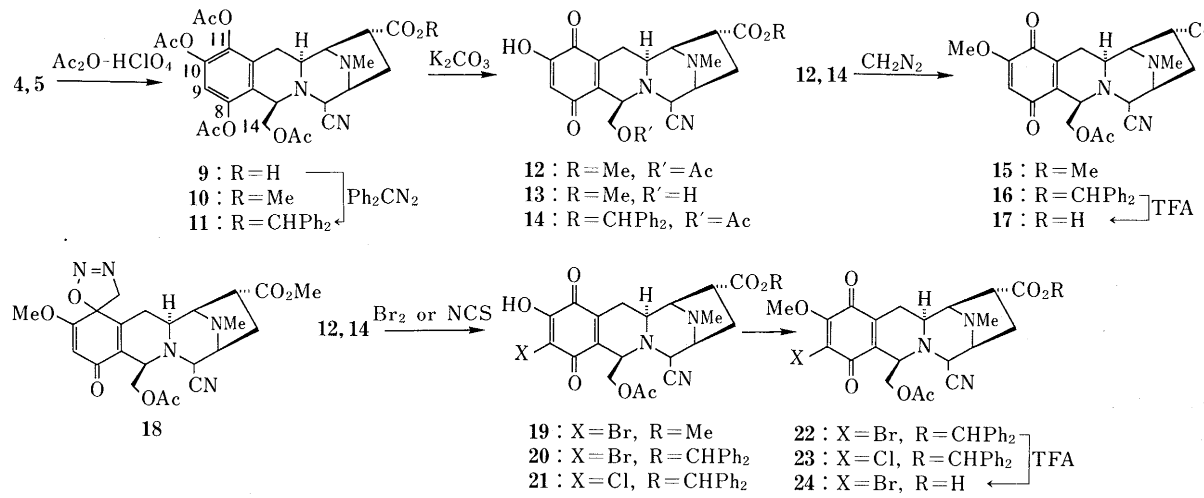


Chart 2

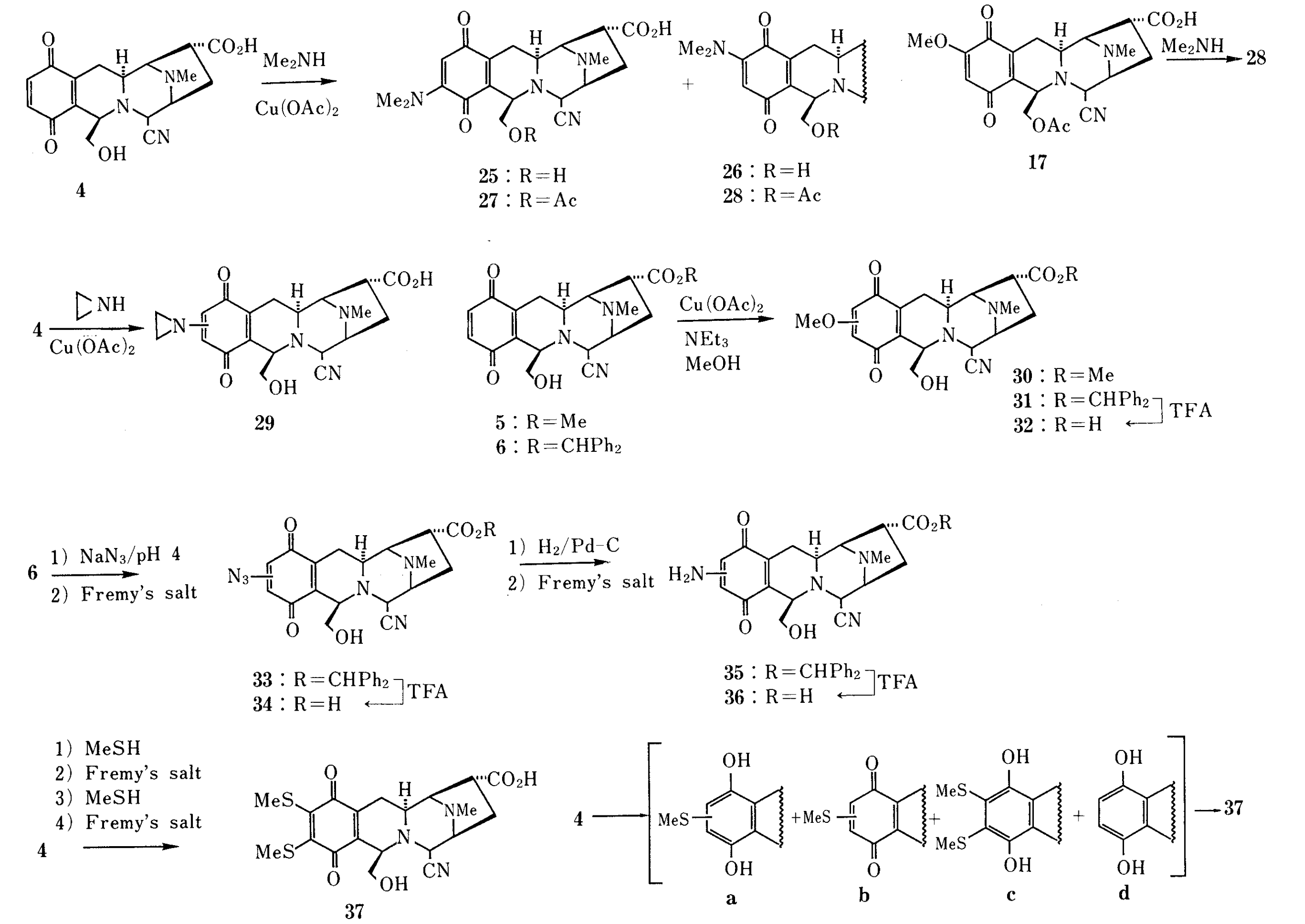


Chart 3

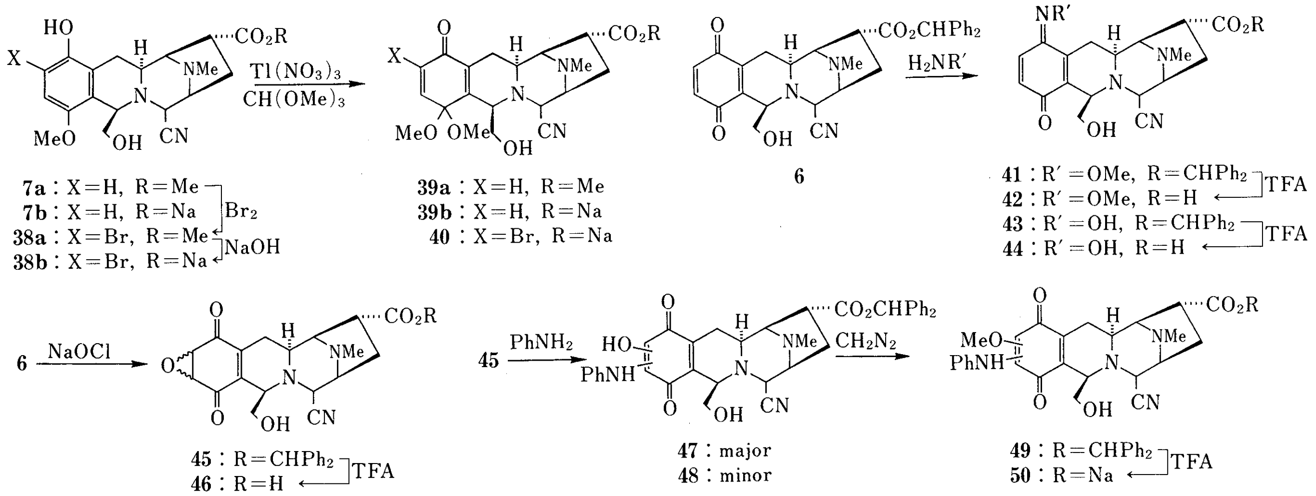


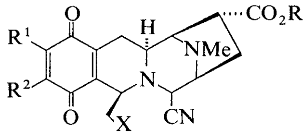
Chart 4

droxyquinones **47** and **48** *via* hydroquinones, while alkylamine could not effect the opening. Although the regiochemistry was uncertain, the major isomer **47** was subjected to methylation followed by ester hydrolysis to give **50**.

Antitumor Activities The obtained compounds were examined for *in vitro* cytotoxicity and several selected substances were subjected to determination of their *in vivo* antileukemic activity. All the analogues were evaluated in the 5-cyano form, which was a little inferior in terms of activity to the corresponding oxazolidine form[2a)] (*e.g.* compare DX-52-1 (**2**)[2)] with quinocarcin (**1**)).

Unexpectedly quinone analogues tended to show decreased antitumor efficiency. As shown in Tables I and II, most of the derivatives exhibited poor cytotoxicity. The simple quinone (**5**) had considerable activity *in vitro*, but it showed no effect *in vivo*. In *in vivo* experiments the methoxyquinone (**17**) was found to have a significant activity only on daily administration, while it was devoid of cytotoxicity *in vitro*. The quinoneoxime (**42**) showed a

TABLE I. Antitumor Activities of Substituted Quinone Analogues



No.	R^1	R^2	X	R	HeLa S_3 IC_{50} (μg/ml)	Dose (mg/kg) × 1	P388 ip-ip ILS (%)	Dose × 5	ILS
4	H	H	OH	H	>10				
5	H	H	OH	Me	0.12	20	18	10	14
12	OH	H	OAc	Me	>10	100	14		
13	OH	H	OH	Me	>10				
15	OMe	H	OAc	Me	0.23				
17	OMe	H	OAc	H	>10	25	22	25	56
24	OMe	Br	OAc	H		9.38	20	9.38	22
32[a]	OMe	H	OH	H	>10	3.13	20	6.25	35
25	H	NMe_2	OH	H	0.92	6.25	12	3.13	9
26	NMe_2	H	OH	H	0.79	3.13	15	6.25	34
34[a]	N_3	H	OH	H	>10	3.13	2	1.56	7
36[a]	H_2N	H	OH	H	>10	1.56	4	1.56	0
37	SMe	SMe	OH	H	0.13	12.5	53	6.25	71
50[b]	PhNH	OMe	OH	H	1.75	100	17		
DX-52-1 (**2**)					0.05	20	26	7.5	62
Quinocarcin (**1**)					0.05—0.11	10—20	24—48	5—10	70—120

a) Regioisomeric mixture. *b*) Regiochemistry was not confirmed.

TABLE II. Antitumor Activities of Other Quinone Analogues

No.	HeLa S_3 IC_{50} (μg/ml)	Dose (mg/kg) × 1	P388 ip-ip ILS (%)	Dose × 5	ILS
39b	>10				
40	1.09				
42	3.0	25	24	25	57
44	>				
50	>10	6.25	15	3.13	15

similar profile to **17**. In contrast to other derivatives the bis-methylthioquinone (**37**) showed significant activity both *in vitro* and *in vivo*. It possessed almost equal cytotoxic potency to **1**. It is noteworthy that **37** exhibited superior activity to **1** in single administration against P388 leukemia. In a sense it was not appropriate to regard these quinone compounds as analogues of quinocarcin. Therefore further evaluation of **37**, and synthetic efforts aimed at other analogues related to **37** are under way.

Experimental

Infrared (IR) spectra were measured with a JASCO IR-810, and NMR spectra were measured on Varian EM-390 (^1H, 90 MHz), JEOL FX-100 (^1H; 100 MHz, ^{13}C; 25 MHz) and Bruker AM-400 (^1H; 400 MHz, ^{13}C; 100 MHz) spectrometers. MS were measured with a Hitachi B-80. For column chromatography, silica gel (SiO_2, Wako C-200) or highly porous polymer resin (Mitsubishi Kasei Diaion HP-20 or HP-20SS) was used. All reactions were monitored by thin-layer chromatography (TLC) using Silica gel 60 F_{254} plate (Merck). All organic solvent extracts were dried over anhydrous sodium sulfate. All aqueous fractions after chromatography were freeze-dried.

Diphenylmethyl 5-Cyano-8-hydroxy-7-hydroxymethyl-13-methyl-1,2,3,4,5,7,12,12a-octahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylate 3c A solution of Ph_2CN_2 (5.4 g) in $CHCl_3$ (25 ml) was added to a solution of **3a** (8.0 g) in $CHCl_3$ (130 ml) and MeOH (35 ml). The mixture was stirred for 1 h 40 min, then further Ph_2CN_2 (4.5 g) in $CHCl_3$ (20 ml) was added and stirring was continued for 1 h. AcOH was added gradually to the reaction mixture until the red purple color had disappeared. The mixture was diluted with $CHCl_3$, washed with saturated $NaHCO_3$ and brine, dried, then concentrated. The residue was subjected to chromatography (SiO_2 500 ml *n*-hexane : AcOEt = 2 : 1) to give **3c** (10.2 g, 86%). ^1H-NMR ($CDCl_3$) ppm: 7.33 (10H, m), 6.97 (1H, m), 6.88 (1H, s), 6.63 (2H, m), 4.18 (1H, m), 3.93 (1H, d), 3.65 (2H, m), 3.44 (1H, br s), 3.38 (1H, m), 3.19 (1H, dd, J=9, 6 Hz), 3.02 (1H, m), 2.47—2.83 (3H, m), 2.11 (3H, s), 1.93 (1H, dd, J=13, 9 Hz). SIMS (m/z): 510 $(M+1)^+$, 483 $(M+1-HCN)^+$.

5-Cyano-8,11-dioxo-7-hydroxymethyl-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylic Acid 4 Method A: The Na salt of **3a** (300 mg, 0.82 mmol) was dissolved in TFA (9 ml) and $Tl(OCOCF_3)_3$ (1.25 g, 2.30 mmol) was added. The reaction mixture was stirred for 2 h and then concentrated. The residue was chromatographed (SiO_2 50 ml, $CHCl_3$: MeOH = 50 : 1—20 : 1) to afford **4** (29.9 mg, 10.2%) as a light brown solid.

Method B: The Na salt of **3a** (8.0 g, 22 mmol) was dissolved in H_2O (800 ml) and 1 N AcONa (25 ml) was added. To this solution, Fremy' salt (20.7 g, 77 mmol) was added gradually followed by stirring for 1.5 h. Then 1 N HCl was added to adjust the pH to 3.5. After concentration the residue was purified by column chromatography (Diaion HP-20 1 l, H_2O : MeOH = 1 : 0—3 : 2) to give **4** (5.12 g, 65.4%). mp 175—180 °C (dec.). *Anal.* Calcd for $C_{18}H_{19}N_3O_5 \cdot H_2O$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.51; H, 5.32; N, 10.83. ^1H-NMR (CD_3OD) ppm: 6.78 (1H, d, J=10.2 Hz), 6.75 (1H, d, J=10.2 Hz), 4.27 (1H, d, J=2.9 Hz), 3.82 (1H, m), 3.79 (1H, dd, J=11.4, 2.3 Hz), 3.61 (1H, dd, J=11.4, 3.7 Hz), 3.52 (1H, dd, J=6.4, 2.6 Hz), 3.51 (1H, br s), 3.22 (1H, dd, J=9.7, 5.9 Hz), 2.78 (1H, m), 2.73 (1H, ddd, J=17.3, 2.9, 1.1 Hz), 2.59 (1H, m), 2.33 (3H, s), 2.15 (1H, ddd, J=17.3, 10.9, 2.6 Hz), 2.02 (1H, dd, J=13.4, 9.7 Hz). ^{13}C-NMR (D_2O) ppm: 187.1, 187.0, 176.2, 141.8, 138.9, 137.8, 137.1, 115.9, 70.2, 65.8, 63.4, 57.3, 55.7, 54.8, 41.0, 40.4, 28.5, 24.2. SIMS (m/z): 360 $(M+3)^+$. IR (KBr): 3430, 1710, 1654, 1457, 1374, 1313, 1207, 1010 cm^{-1}.

Methyl 5-Cyano-8,11-dioxo-7-hydroxymethyl-13-methyl-1,2,3,4,5,7,8,-11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylate 5 Method A: $Tl(OCOCF_3)_3$ (1.55 g, 2.86 mmol) was added to a solution of **3b** (424 mg, 1.19 mmol) in TFA (12 ml), and the mixture was stirred for 4.5 h, then concentrated. The residue was dissolved in AcOEt and the solution was washed with aqueous $NaHCO_3$ and brine, then dried. After concentration the residue was chromatographed (SiO_2 60 ml, *n*-hexane : AcOEt = 2 : 1—1 : 1) to give **5** (71.2 mg, 16.2%) as a light brown solid.

Method B: To a solution of **3b** (2.06 g, 5.76 mmol) in CH_3CN (90 ml) was added 1 N AcONa (19 ml) and H_2O (350 ml). After gradual addition of Fremy's salt (7.7 g, 28.8 mmol), the mixture was stirred for 1 h 50 min. The pH was adjusted at 7.3 with saturated $NaHCO_3$, and the mixture was extracted with AcOEt three times. The combined extracts were washed with brine, dried, and concentrated to provide **5** (1.60 g, 75.0%). mp 168—173 °C (dec.). ^{1}H-NMR ($CDCl_3$) ppm: 6.73 (2H, s), 4.00 (1H, d, $J=3$ Hz), 3.93 (1H, m), 3.73 (3H, s), 3.63—3.77 (1H, m), 3.43—3.60 (2H, m), 3.47 (1H, br s), 2.47—3.13 (4H, m), 2.33 (3H, s), 2.17 (1H, m), 1.88 (1H, dd, $J=13$, 10 Hz). ^{13}C-NMR ($CDCl_3$) ppm: 185.4, 185.2, 175.3, 141.4, 138.8, 137.0, 136.1, 116.7, 69.8, 64.5, 63.1, 57.6, 56.6, 56.0, 52.4, 42.7, 41.8, 28.9, 25.0. EIMS (*m/z*): 371 (M^+), 340 $(M-OMe)^+$, 279, 201, 180, 140. IR (KBr): 3500, 2956, 1733, 1654, 1605, 1458, 1438, 1313, 1205, 1182, 1073 cm^{-1}.

Diphenylmethyl 5-Cyano-8,11-dioxo-7-hydroxymethyl-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylate 6 First 1 N AcONa (10 ml) and H_2O (160 ml) were added to a solution of **3c** (1.43 g, 2.81 mmol) in CH_3CN (100 ml), then Fremy's salt (4.5 g) was added in three portions in 5 h under stirring. The reaction mixture was extracted with AcOEt. The AcOEt layer was washed with brine, dried and then concentrated. The residue was subjected to chromatography (SiO_2 220 ml, $CHCl_3$: MeOH = 1 : 0—50 : 1) to afford **6** (1.16 g, 78.8%) as a pale brown solid along with **3c** (127 mg, 8.9%). mp 160—165 °C (dec.). *Anal.* Calcd for $C_{31}H_{29}N_3O_5 \cdot 0.5H_2O$: C, 69.91; H, 5.68; N, 7.89. Found: C, 70.00; H, 5.53; N, 7.71. ^{1}H-NMR ($CDCl_3$) ppm: 7.25—7.43 (10H, m), 6.89 (1H, s), 6.72 (2H, s), 3.87—4.03 (2H, m), 3.73 (2H, m), 3.52 (1H, br s), 3.45 (1H, m), 2.50—3.23 (4H, m), 2.12—2.33 (1H, m), 2.14 (3H, s), 1.93 (1H, dd, $J=13$, 10 Hz). SIMS (*m/z*): 526 $(M+3)^+$, 499 $(M+3-HCN)^+$. IR (KBr): 3470, 2952, 1728, 1654, 1603, 1494, 1455, 1310, 1171 cm^{-1}.

Methyl 5-Cyano-8,11-dioxo-7-hydroxymethyl-13-methyl-1,2,3,4,5,7,8,-11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylate 5 and Methyl 5-Cyano-8-methoxy-13-methyl-11-oxo-1,2,3,4,5,7,8,11,12,12a-decahydro-8,7-epoxymethano-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylate 8 $NaIO_4$ (612 mg, 2.9 mmol) in H_2O (20 ml) was added dropwise to a solution of **7a**[2a] (1.0 g, 2.6 mmol) in CH_3CN (20 ml), and the mixture was stirred for 45 min. Brine was added and the whole was extracted with AcOEt. After drying of the extract and evaporation, the residue was chromatographed (SiO_2 100 ml, *n*-hexane : AcOEt = 1 : 1—0 : 1) to give **5** (243 mg, 25.3%) and **8** (46.3 mg, 4.7%), each as a light brown solid. **8**: mp 85—86 °C. ^{1}H-NMR ($CDCl_3$) ppm: 6.96 (1H, d, $J=10.1$ Hz), 6.26 (1H, d, $J=10.1$ Hz), 4.46 (1H, t, $J=7.8$ Hz), 4.11 (1H, m), 3.83 (1H, dd, $J=8.0$, 5.6 Hz), 3.72 (3H, s), 3.57 (1H, d, $J=2.8$ Hz), 3.52 (1H, m), 3.46 (1H, br s), 3.31 (3H, s), 3.08 (1H, ddd, $J=10.0$, 5.3, 1.7 Hz), 2.97 (1H, dd, $J=9.5$, 5.8 Hz), 2.65 (1H, m), 2.59 (1H, ddd, $J=18.6$, 5.3, 3.3 Hz), 2.34 (3H, s) 2.14 (1H, ddd, $J=18.6$, 10.0, 2.7 Hz), 1.89 (1H, dd, $J=13.5$, 9.6 Hz). ^{13}C-NMR ($CDCl_3$) ppm: 184.3, 175.3, 150.0, 139.1, 130.5, 126.2, 115.6, 96.9, 73.6, 69.9, 64.5, 58.3, 57.6, 56.1, 52.4, 50.5, 42.9, 41.8, 28.5, 24.5. EIMS (*m/z*): 385 (M^+), 354 $(M-OMe)^+$, 207, 180, 140, 121. IR (KBr): 2954, 1728, 1663, 1616, 1458, 1435, 1365, 1348, 1328, 1207, 1181, 1135, 1056 cm^{-1}.

7-Acetoxymethyl-5-cyano-13-methyl-8,10,11-triacetoxy-1,2,3,4,5,7,-12,12a-octahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylic Acid 9 A 70% $HClO_4$ solution (0.3 ml) was added to a solution of **4** (600 mg) in Ac_2O (15 ml), followed by stirring for 19 h, and evaporation. Ice was added to the residue. The mixture was extracted with AcOEt three times, and the combined extracts were washed with brine, dried and then evaporated. The residue was purified by column chromatography (SiO_2 50 ml, $CHCl_3$: MeOH = 1 : 0—50 : 1) to give **9** (542 mg, 59.4%). ^{1}H-NMR ($CDCl_3$) ppm: 7.09 (1H, s), 4.32 (1H, dd, $J=11.1$, 3.4 Hz), 4.24 (1H, dd, $J=5.7$, 3.4 Hz), 3.88 (1H, d, $J=2.8$ Hz), 3.86 (1H, dd, $J=11.1$, 5.7 Hz), 3.50 (2H, m), 3.09 (1H, dd, $J=9.4$, 5.7 Hz), 3.04 (1H, br d, $J=11.5$ Hz), 2.65 (1H, dd, $J=15.3$, 2.2 Hz), 2.59 (1H, m), 2.38 (3H, s), 2.328 (3H, s), 2.325 (3H, s), 2.28 (3H, s), 2.04 (3H, s), 2.00 (1H, dd, $J=13.0$, 9.4 Hz). SIMS (*m/z*): 544 $(M+1)^+$, 517 $(M+1-HCN)^+$, 475, 459, 445.

Methyl 7-Acetoxymethyl-5-cyano-13-methyl-8,10,11-triacetoxy-1,2,3,4,-5,7,12,12a-octahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylate 10 In the same manner as described for **9**, **5** yielded **10** (315 mg, 71.1%) as a white solid. mp 94—95 °C. *Anal.* Calcd for $C_{27}H_{31}N_3O_{10} \cdot H_2O$: C, 56.34; H, 5.78; N, 7.30. Found: C, 56.45; H, 5.58; N, 7.12. ^{1}H-NMR ($CDCl_3$) ppm: 7.08 (1H, s), 4.10—4.40 (3H, m), 3.77—3.97 (2H, m), 3.72 (3H, s), 3.30—3.53 (2H, m), 2.83—3.13 (2H, m), 2.47—2.80 (2H, m), 2.30 (9H, s), 2.24 (3H, s), 2.00 (3H, s), 1.80—2.10 (1H, m). EIMS (*m/z*): 557 (M^+), 526, 484, 442, 400, 378, 345, 180, 140, 121. High-resolution EIMS: Calcd for $C_{27}H_{31}N_3O_{10}$: 557.2006. Found: 557.1992. IR (KBr): 3430, 1775, 1736, 1617, 1477, 1436, 1371, 1179 cm^{-1}.

Diphenylmethyl 7-Acetoxymethyl-5-cyano-13-methyl-8,10,11-triacetoxy-1,2,3,4,5,7,12,12a-octahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylate 11 In the same manner as described for **3c**, **9** (165 mg) gave **11** (174 mg, 80.8%). ^{1}H-NMR ($CDCl_3$) ppm: 7.33 (10H, m), 7.07 (1H, s), 6.87 (1H, s), 4.13—4.47 (2H, m), 3.73—4.00 (2H, m), 3.43 (2H, m), 2.90—3.27 (2H, m), 2.43—2.80 (2H, m), 2.30 (3H, s), 2.25 (6H, s), 2.13 (3H, s), 2.00 (3H, s), 1.82 (1H, m). IR (KBr): 3450, 1773, 1730, 1615, 1480, 1425, 1355, 1220, 1175, 1060, 1020, 740, 699 cm^{-1}. SIMS (*m/z*): 710 $(M+1)^+$, 683 $(M+3-HCN)^+$.

Methyl 7-Acetoxymethyl-5-cyano-8,11-dioxo-10-hydroxy-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylate 12 and Methyl 5-Cyano-8,11-dioxo-10-hydroxy-7-hydroxymethyl-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino-[1,2-*b*]isoquinoline-2-carboxylate 13 K_2CO_3 (186 mg, 1.34 mmol) was added to a solution of **10** (250 mg, 0.45 mmol) in a mixture of MeOH (2.5 ml) and H_2O (2 ml). The mixture was stirred for 30 min, adjusted pH to 3—4 with 6 N HCl, and concentrated, followed by chromatography (Diaion HP-20 20 ml, H_2O : acetone = 1 : 0—3 : 2) of the residue to give **12** (90.0 mg, 46.7%) and **13** (41.1 mg, 23.7%), each as an orange solid. **12**; mp 121—125 °C (dec.). *Anal.* Calcd for $C_{21}H_{23}N_3O_7 \cdot 1.5H_2O$: C, 55.26; H, 5.74; N, 9.21. Found: C, 55.08; H, 5.74; N, 9.03. ^{1}H-NMR ($CDCl_3$) ppm: 6.11 (1H, s), 4.71 (1H, dd, $J=11.8$, 3.0 Hz), 4.07 (1H, m), 4.01 (1H, dd, $J=11.8$, 2.8 Hz), 3.99 (1H, d, $J=3.0$ Hz), 3.74 (3H, s), 3.49 (1H, m), 3.44 (1H, br s), 2.92 (1H, m), 2.83 (1H, dd, $J=9.7$, 5.7 Hz), 2.77 (1H, ddd, $J=17.6$, 3.0, 1.3 Hz), 2.57 (1H, m), 2.34 (3H, s), 2.01 (3H, s), 1.98—2.07 (1H, m), 1.96 (1H, dd, $J=13.6$, 9.7 Hz). ^{13}C-NMR (D_2O) ppm: 187.4, 187.2, 178.7, 174.6, 172.1, 141.2, 138.6, 118.8, 69.8, 65.3, 64.9, 57.0, 56.7, 56.1, 53.6, 43.0, 41.6, 28.9, 25.1, 21.0. ^{13}C-NMR ($CDCl_3$) ppm: 185.1, 182.1, 175.4, 170.4, 154.1, 140.7, 137.6, 116.7, 108.6, 69.7, 64.7, 62.5, 56.2, 56.1, 55.9, 52.4, 42.5, 41.8, 28.4, 24.6, 20.8. SIMS (*m/z*): 432 $(M+3)^+$, 405 $(M+3-HCN)^+$. IR (KBr): 3430, 2956, 1730, 1662, 1629, 1557, 1458, 1368, 1259, 1229, 1180, 1041 cm^{-1}. **13**; mp 128–132 °C (dec.). ^{1}H-NMR ($CDCl_3$) ppm: 6.10 (1H, s), 4.05 (1H, m), 4.00 (1H, d, $J=3$ Hz), 3.75 (3H, s), 3.70 (1H, m), 3.42—3.65 (3H, m), 2.91 (1H, m), 2.80 (1H, dd, $J=10$, 6 Hz), 2.42—2.85 (2H, m), 2.33 (3H, s), 2.02 (1H, m), 1.98 (1H, dd, $J=13$, 10 Hz). SIMS (*m/z*): 390 $(M+3)^+$, IR (KBr): 3430, 2956, 1730, 1659, 1628, 1457, 1436, 1365, 1226, 1180, 1039 cm^{-1}.

Diphenylmethyl 7-Acetoxymethyl-5-cyano-8,11-dioxo-10-hydroxy-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]iso-quinoline-2-carboxylate 14 A 1 M K_2CO_3 solution (0.39 ml) was added portionwise over 4.5 h to a solution of **11** (160 mg, 0.225 ml) in MeOH (10 ml) under stirring. After addition of pH 4.0 acetate buffer, MeOH was distilled off followed by extraction with AcOEt. The extract was washed with brine, dried and evaporated. Purification of the residue by chromatography (SiO_2 13 ml, $CHCl_3$: MeOH = 1 : 0—100 : 1) yielded **14** (86.7 mg, 66.1%) as an orange solid. mp 105—106 °C. ^{1}H-NMR ($CDCl_3$) ppm: 7.18—7.38 (10H, m), 6.89 (1H, s), 6.11 (1H, s), 4.70 (1H, dd, $J=11.8$, 3.1 Hz), 4.07 (1H, m), 4.01 (1H, dd, $J=11.8$, 2.9 Hz), 3.99 (1H, d, $J=3.1$ Hz), 3.45 (1H, m), 3.45 (1H, br s), 2.93 (1H, dd, $J=9.6$, 6.1 Hz), 2.92 (1H, m), 2.80 (1H, ddd, $J=17.5$, 3.0, 1.3 Hz), 2.57 (1H, ddd, $J=13.3$, 6.9, 6.2 Hz), 2.15 (3H, s), 2.08 (1H, ddd, $J=17.5$, 11.0, 3.0 Hz), 1.99 (3H, s), 1.99 (1H, dd, $J=13.3$, 9.6 Hz). SIMS (*m/z*): 584 $(M+3)^+$, 557 $(M+3-HCN)^+$, 510. IR (KBr): 3400, 2954, 1731, 1660, 1631, 1495, 1455, 1411, 1367, 1319, 1221, 1171, 1043 cm^{-1}.

Methyl 7-Acetoxymethyl-5-cyano-8,11-dioxo-10-methoxy-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylate 15 CH_2N_2 in ether was added gradually to a solution of **12** (30 mg) in MeOH (3 ml) and the mixture was stirred until the red–purple color had disappeared. After bubbling with N_2, the reaction mixture was concentrated. Purification of the residue by chromatography (SiO_2 10 ml, *n*-hexane : AcOEt = 1 : 1) gave **15** (15.4 mg, 49.7%). ^{1}H-NMR ($CDCl_3$) ppm: 5.93 (1H, s), 4.68 (1H, dd, $J=11.2$, 2.4 Hz), 4.05 (1H, m), 4.03 (1H, m), 3.99 (1H, d, $J=2.8$ Hz), 3.85 (3H, s), 3.73 (3H, s), 3.49 (1H, m), 3.44 (1H, br s), 2.89 (1H, m), 2.83 (1H, dd, $J=9.7$, 5.9 Hz), 2.80 (1H, m), 2.57 (1H, m), 2.34 (3H, s), 2.00 (3H, s), 2.00 (1H, m), 1.95 (1H, dd, $J=13.4$, 9.6 Hz). ^{13}C-NMR ($CDCl_3$) ppm: 184.9, 180.4, 175.5, 170.5, 158.4, 139.5, 138.7, 116.8, 107.9, 69.8, 64.7, 62.5, 56.4, 56.2, 56.2, 55.7, 52.4, 42.5, 41.8, 28.4, 24.8, 20.9. SIMS (*m/z*): 446 $(M+3)^+$, 419 $(M+3-HCN)^+$. IR (KBr): 1735, 1654, 1637, 1612, 1228 cm^{-1}.

Diphenylmethyl 7-Acetoxymethyl-5-cyano-8,11-dioxo-10-methoxy-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquino-line-2-carboxylate 16 In the same manner as described for **15**, **14** (450 mg) afforded **16** (392 mg. 85.1%) as a yellow solid. mp 180—185 °C (dec.). ^{1}H-NMR ($CDCl_3$) ppm: 7.28—7.38 (10H, m), 6.88 (1H, s), 5.93 (1H, s), 4.69 (1H, dd, $J=11.6$, 2.7 Hz), 4.06 (1H, m), 4.03 (1H, dd, $J=11.6$, 2.8 Hz), 3.99 (1H, br s), 3.85 (3H, s), 3.46 (1H, br s), 3.46 (1H, m), 2.94 (1H, dd, $J=9.3$, 6.0 Hz), 2.91 (1H, m), 2.84 (1H, dd, $J=17.6$, 2.0 Hz), 2.56 (1H, m), 2.15 (3H, s), 2.06 (1H, ddd, $J=17.6$, 10.9, 2.7 Hz), 1.98 (3H, s), 1.98

(1H, m). SIMS (m/z): 598 $(M+3)^+$, 571 $(M+3-HCN)^+$. IR (KBr): 1740, 1734, 1675, 1659, 1633, 1608, 1494, 1455, 1355, 1295, 1223, 1172, 1057, 1021 cm^{-1}.

7-Acetoxymethyl-5-cyano-8,11-dioxo-10-methoxy-13-methyl-1,2,3,4,5,-7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylic Acid 17 Anisole (2 ml) and TFA (1.5 ml) were added to a solution of **16** (390 mg) in CH_2Cl_2 (20 ml), and the mixture was stirred for 1 h, then concentrated. The residue was subjected to chromatography (Diaion HP-20 30 ml, H_2O : MeOH = 1 : 0—2 : 3) to give **17** (217 mg, 77.3%) as a pale yellow solid. mp 134—137 °C (dec.). *Anal.* Calcd for $C_{21}H_{23}N_3O_7 \cdot 0.5H_2O$: C, 57.53; H, 5.52; N, 9.58. Found: C, 57.64; H, 5.76; N, 9.37. ^{1}H-NMR (D_2O) ppm: 6.09 (1H, s), 4.70 (1H, d, J = 2.5 Hz), 4.55 (1H, dd, J = 11.5, 2.8 Hz), 4.36 (1H, br d, J = 6.5 Hz), 4.21 (1H, br s), 4.17—4.20 (2H, m), 3.86 (3H, s), 3.15—3.19 (2H, m), 2.93 (1H, dd, J = 17.3, 2.8 Hz), 2.78 (3H, s), 2.71 (1H, m), 2.30 (1H, dd, J = 14.5, 10.5 Hz), 2.25 (1H, m), 2.05 (3H, s). ^{13}C-NMR (D_2O) ppm: 187.2, 181.7, 179.3, 174.5, 159.6, 139.9, 138.8, 116.4, 108.2, 70.8, 65.8, 64.7, 57.4, 55.4, 55.0, 55.0, 42.7, 41.1, 29.0, 24.2, 20.9. SIMS (m/z): 432 $(M+3)^+$, 405 $(M+3-HCN)^+$. IR (KBr): 3450, 1735, 1678, 1660, 1631, 1611, 1457, 1228 cm^{-1}.

Methyl 7-Acetoxymethyl-5-cyano-8,11-dioxo-10-methoxy-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-11-spiro-5′-[4′,5′-dihydro-1′,2′,3′-oxadiazole]-2-carboxylate 18 Except for excess CH_2N_2 addition, **12** (240 mg) provided **18** (130 mg, 48.1%) in the same manner as described for **15**. ^{1}H-NMR ($CDCl_3$) ppm: 5.80 and 5.79 (1H, s), 4.58 (0.5H, dd, J = 11.3, 2.8 Hz), 4.57 (0.5H, dd, J = 11.5, 2.8 Hz), 4.10 and 4.07 (1H, m), 4.021 (0.5H, dd, J = 11.3, 3.9 Hz), 4.017 (0.5H, dd, J = 11.5, 3.4 Hz), 3.97 and 3.96 (1H, d, J = 2.9 Hz), 3.78 and 3.77 (3H, s), 3.72 (3H, s), 3.58 (0.5H, d, J = 6.4 Hz), 3.51 (0.5H, d, J = 6.3 Hz), 3.45 (1H, m), 3.37 (1H, br s), 3.27 (0.5H, d, J = 6.3 Hz), 3.21 (0.5H, d, J = 6.4 Hz), 2.90 (1H, m), 2.84 (1H, m), 2.319 and 2.316 (3H, s), 2.24 (0.5H, dd, J = 16.3, 2.2 Hz), 2.023 and 2.018 (3H, s), 1.94 (1H, m), 1.79 (1H, m). ^{13}C-NMR ($CDCl_3$) ppm: 183.73, 183.65, 175.61, 175.56, 170.6, 170.5, 168.3, 167.9, 146.0, 145.1, 133.6, 133.5, 117.1, 105.9, 105.3, 69.90, 69.88, 64.7, 63.8, 63.1, 56.8, 56.7, 56.6, 56.3, 56.2, 55.7, 55.4, 53.3, 52.8, 52.5, 52.4, 52.1, 42.7, 42.5, 41.9, 41.8, 28.6, 28.5, 24.5, 24.4, 21.0. EIMS (m/z): 457 $(M-N_2)^+$, 426, 384, 245, 180, 140, 121. SIMS (m/z): 460 $(M+3-N_2)^+$, 458, 433, 431, 415, 386.

Methyl 7-Acetoxymethyl-9-bromo-5-cyano-8,11-dioxo-10-hydroxy-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylate 19 A 1 M $Br_2/CHCl_3$ solution (0.25 ml) was added to a solution of **12** (100 mg, 0.23 mmol) in $CHCl_3$ under ice-cooling. The mixture was stirred for 2.5 h at 0 °C. Acetate buffer (pH 4.0) was added and the mixture was extracted with $CHCl_3$ five times. The combined extracts were washed with brine, dried and concentrated. Purification by chromatography (SiO_2 10 ml, $CHCl_3$: MeOH = 1 : 0—50 : 1) gave **19** (79.1 mg, 66.8%) as a red-purple solid. mp 124—127 °C (dec.). *Anal.* Calcd for $C_{21}H_{22}BrN_3O_7 \cdot 0.5H_2O$: C, 48.76; H, 4.48; N, 8.12. Found: C, 48.83; H, 4.83; N, 7.96. ^{1}H-NMR ($CDCl_3$–CD_3OD) ppm: 4.64—4.84 (1H, m), 4.00—4.24 (3H, m), 3.77 (3H, s), 3.46—3.64 (2H, m), 2.44—3.08 (4H, m), 2.38 (3H, s), 2.06 (3H, s), 1.98 (1H, m). SIMS (m/z): 510, 512 $(M+3)^+$, 483, 485 $(M+3-HCN)^+$, 432, 405. IR (KBr): 3516, 3478, 2954, 1740, 1720, 1667, 1624, 1540, 1474, 1434, 1360, 1281, 1225 cm^{-1}.

Diphenylmethyl 7-Acetoxymethyl-9-chloro-5-cyano-8,11-dioxo-10-hydroxy-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino-[1,2-*b*]isoquinoline-2-carboxylate 21 NCS (84 mg, 0.63 mmol) in CH_2Cl_2 (2 ml) was added portionwise to a solution of **14** (300 mg, 0.52 mmol) in CH_2Cl_2 (10 ml) over 3 h under ice-cooling. The mixture was diluted with $CHCl_3$, washed with H_2O and brine, then dried and concentrated. The residue was chromatographed (SiO_2 40 ml, $CHCl_3$: MeOH = 1 : 0—100 : 1) to afford **21** (117 mg, 52.6%). ^{1}H-NMR ($CDCl_3$) ppm: 7.38 (10H, m), 6.94 (1H, s), 4.60—5.08 (2H, m), 4.06 (3H, m), 3.52 (2H, m), 2.44—3.12 (3H, m), 2.16 (3H, s), 1.99 (3H, s). SIMS (m/z): 618 $(M+3)^+$, 591 $(M+3-HCN)^+$. IR (KBr): 3410, 1738, 1657, 1629, 1539, 1494, 1454, 1358, 1227, 1169 cm^{+1}.

Diphenylmethyl 7-Acetoxymethyl-9-bromo-5-cyano-8,11-dioxo-10-methoxy-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino-[1,2-*b*]isoquinoline-2-carboxylate 22 Bromination of **14** (290 mg) followed by methylation with CH_2N_2, in the same manner as described for **19** and **15**, respectively, gave **22** (299 mg, 88.8%). ^{1}H-NMR ($CDCl_3$) ppm: 7.25—7.50 (10H, m), 6.98 (1H, s), 4.70 (1H, m), 4.21 (3H, s), 3.88—4.10 (3H, m), 3.45 (2H, m), 2.40—3.05 (4H, m), 2.15 (3H, s), 2.00 (3H, s), 1.82—2.10 (2H, m). SIMS (m/z): 676, 678 $(M+3)^+$, 649, 651 $(M+3-HCN)^+$, 598, 571. IR (KBr): 1725, 1660, 1592, 1494, 1445, 1320, 1281, 1222, 1170 cm^{-1}.

Diphenylmethyl 7-Acetoxymethyl-9-chloro-5-cyano-8,11-dioxo-10-methoxy-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino-[1,2-*b*]isoquinoline-2-carboxylate 23 By a similar procedure to that described for **15**, **21** (144 mg) yielded **23** (119 mg, 80.8%) as a yellow-brown solid. mp 113—115 °C. *Anal.* Calcd for $C_{34}H_{32}ClN_3O_7 \cdot 2.5H_2O$: C, 60.49; H, 5.52; N, 6.22. Found: C, 60.58; H, 5.25; N, 6.47. ^{1}H-NMR ($CDCl_3$) ppm: 7.36 (10H, m), 6.92 (1H, s), 4.72 (1H, m), 4.24 (3H, s), 3.96—4.12 (3H, m), 3.48 (2H, m), 2.92 (2H, m), 2.44—2.80 (2H, m), 2.16 (3H, s), 2.00 (3H, s), 1.84—2.08 (2H, m). SIMS (m/z): 632 $(M+3)^+$, 605 $(M+3-HCN)^+$. IR (KBr): 1722, 1664, 1595, 1494, 1454, 1323, 1273, 1224, 1172 cm^{-1}.

7-Acetoxymethyl-9-bromo-5-cyano-8,11-dioxo-10-methoxy-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylic Acid 24 In the same manner as described for **17**, **22** (100 mg) provided **24** (49.7 mg, 66.0%) as a lyophilized solid. mp 133—137 °C (dec.). *Anal.* Calcd for $C_{21}H_{22}BrN_3O_7 \cdot H_2O$: C, 47.92; H, 4.60; N, 7.98. Found: C, 47.97; H, 4.32; N, 7.81. ^{1}H-NMR ($CDCl_3$–CD_3OD) ppm: 4.66 (1H, dd, J = 12.6, 3.9 Hz), 4.51 (1H, m), 4.24 (3H, s), 4.10 (1H, d, J = 2.6 Hz), 4.05 (1H, m), 3.52 (2H, m), 2.80—2.90 (3H, m), 2.58 (1H, m), 2.37 (3H, s), 2.07 (1H, m), 2.04 (3H, s), 1.95 (1H, dd, J = 13.5, 9.7 Hz). ^{13}C-NMR ($CDCl_3$–CD_3OD) ppm: 179.7, 179.0, 177.4, 171.4, 157.4, 140.6, 138.1, 118.5, 117.2, 70.1, 65.0, 63.0, 61.9, 56.6, 56.5, 56.3, 42.7, 41.9, 28.5, 25.2, 20.9. SIMS (m/z): 510, 512 $(M+3)^+$, 483, 485 $(M+3-HCN)^+$. IR (KBr): 3400, 1734, 1665, 1589, 1447, 1374, 1225 cm^{-1}.

5-Cyano-9-dimethylamino-8,11-dioxo-7-hydroxymethyl-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylic Acid 25 and 5-Cyano-10-dimethylamino-8,11-dioxo-7-hydroxymethyl-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino-[1,2-*b*]isoquinoline-2-carboxylic Acid 26 $Me_2NH \cdot HCl$ (457 mg), K_2CO_3 (232 mg) and $Cu(OAc)_2 \cdot H_2O$ (224 mg) were dissolved in MeOH (13 ml), and then a solution of **4** (400 mg) in MeOH (26 ml) was added dropwise. The mixture was stirred for 40 min in an oxygen atmosphere. Acetate buffer (pH 4.0) was added and MeOH was distilled off. The resultant mixture was subjected to chromatography (Diaion HP-20 70 ml, H_2O : MeOH = 1 : 0—1 : 1) to give a mixture of **25** and **26** (344 mg), which was separated by preparative HPLC (Nucleosil $_{10}C_{18}$, 20 × 250 mm, 10% CH_3CN/0.01 M $AcONH_4$) to afford **25** (170 mg, 38%) and **26** (131 mg, 29%), each as a red–purple lyophilized solid. **25**; mp 155—160 °C (dec.). ^{1}H-NMR (D_2O) ppm: 5.55 (1H, s), 4.60 (1H, d, J = 2.5 Hz), 4.15 (1H, m), 4.03 (1H, br s), 3.96 (1H, m), 3.80 (1H, dd, J = 12.1, 2.4 Hz), 3.65 (1H, dd, J = 12.1, 3.6 Hz), 3.20–3.28 (1H, m), 3.17 (6H, s), 3.06 (1H, br d, J = 9.3 Hz), 2.80 (1H, m), 2.64–2.70 (1H, m), 2.64 (3H, s), 2.28 (1H, m), 2.20 (1H, m). ^{13}C-NMR (D_2O) ppm: 184.3, 183.7, 153.7, 143.8, 136.6, 117.4, 101.1, 70.8, 65.6, 62.7, 57.7, 56.6, 55.7, 43.3, 43.3, 41.3, 29.6, 25.2. SIMS (m/z): 403 $(M+3)^+$. IR (KBr): 3420, 1706, 1658, 1567, 1395, 1284, 1175 cm^{-1}. **26**; mp 143—148 °C (dec.). ^{1}H-NMR (D_2O) ppm: 5.51 (1H, s), 4.55 (1H, d, J = 2.7 Hz), 4.08 (1H, m), 3.96 (1H, br s), 3.89 (1H, m), 3.85 (1H, dd, J = 11.8, 2.4 Hz), 3.67 (1H, dd, J = 11.8, 3.4 Hz), 3.18—3.23 (1H, m), 3.17 (6H, s), 3.00 (1H, br d, J = 9.0 Hz), 2.79 (1H, m), 2.65 (1H, m), 2.58 (3H, s), 2.24 (1H, dd, J = 14.1, 10.4 Hz), 2.17 (1H, ddd, J = 17.2, 10.8, 2.3 Hz). ^{13}C-NMR (D_2O) ppm: 184.4, 184.2, 153.2, 140.1, 139.5, 117.6, 101.5, 70.8, 65.6, 63.4, 58.1, 56.7, 56.0, 43.2, 43.2, 41.4, 29.6, 25.1. SIMS (m/z): 403 $(M+3)^+$, 376 $(M+3-HCN)^+$. IR (KBr): 3430, 1707, 1662, 1566, 1399, 1293, 1178 cm^{-1}.

7-Acetoxymethyl-5-cyano-9-dimethylamino-8,11-dioxo-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylic Acid 27 A solution of **25** (30 mg) in pyridine (1 ml) and acetic anhydride (0.2 ml) was stirred for 2 h. After concentration, acetate buffer (pH 4.0) and NaCl were added. The mixture was extracted with AcOEt twice. The combined extracts were washed with brine, dried and concentrated. The residue was subjected to chromatography (SiO_2 10 ml, $CHCl_3$: MeOH = 1 : 0—50 : 1) to give **27** (27.0 mg, 81.5%) as a red-purple solid. mp 127—128 °C. ^{1}H-NMR ($CDCl_3$) ppm: 5.59 (1H, s), 4.46 (1H, dd, J = 11.8, 2.8 Hz), 4.12 (1H, dd, J = 11.8, 2.9 Hz), 4.05 (1H, m), 3.98 (1H, d, J = 2.8 Hz), 3.51 (1H, m), 3.50 (1H, br s), 3.15 (6H, s), 2.94 (1H, dd, J = 9.5, 5.9 Hz), 2.86 (2H, m), 2.57 (1H, ddd, J = 13.3, 6.7, 6.2 Hz), 2.39 (3H, s), 2.01 (3H, s), 2.00 (1H, m), 1.96 (1H, dd, J = 13.3, 9.5 Hz). SIMS (m/z): 445 $(M+3)^+$, 418 $(M+3-HCN)^+$. IR (KBr): 3430, 2954, 1735, 1662, 1600, 1571, 1457, 1436, 1379, 1351, 1278, 1228, 1178, 1135, 1043 cm^{-1}.

7-Acetoxymethyl-5-cyano-10-dimethylamino-8,11-dioxo-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylic Acid 28 In the same manner as described for **27**, **26** (30 mg) gave **28** (23.2 mg, 70.0%) as a red–purple solid. mp 118—119 °C. ^{1}H-NMR ($CDCl_3$) ppm: 5.56 (1H, s), 4.74 (1H, dd, J = 12.6, 3.9 Hz), 4.09 (1H, s), 4.07 (1H, m), 4.00 (1H, d, J = 2.8 Hz), 3.50 (1H, dd, J = 6.3, 2.5 Hz), 3.47

(1H, br s), 3.15 (6H, s), 2.91 (1H, m), 2.88 (1H, m), 2.73 (1H, dd, J=17.4, 2.4 Hz), 2.53 (1H, ddd, J=13.4, 6.7, 6.3 Hz), 2.39 (3H, s), 2.02 (3H, s), 1.99 (1H, dd, J=13.4, 9.5 Hz), 1.96 (1H, m). SIMS (m/z): 445 $(M+3)^+$, 418 $(M+3-HCN)^+$, 371. IR (KBr): 3430, 2952, 1735, 1664, 1600, 1570, 1458, 1400, 1374, 1295, 1261, 1227, 1179, 1152, 1044 cm^{-1}.

A Mixture of 9-Aziridino-5-cyano-8,11-dioxo-7-hydroxymethyl-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylic Acid and the 10-Aziridino Isomer 29 $Cu(OAC)_2 \cdot H_2O$ (230 mg) was suspended in MeOH (6 ml), and then an aqueous solution of aziridine (prepared from 2-bromoethylamine and NaOH in H_2O) and a solution of **4** (200 mg, 0.56 mmol) in MeOH (12 ml) were added. The mixture was stirred for 20 min, then pH 4.0 acetate buffer (20 ml) was added and MeOH was distilled off. The resultant aqueous solution was chromatographed (Diaion HP-20 40 ml, H_2O:MeOH=1:0—7:3) to give crude **29** (130 mg), which was further purified by chromatography (SiO_2 20 ml, $CHCl_3$:MeOH=1:0—10:1) to yield **29** (37.4 mg, 16.8%). ^{1}H-NMR (D_2O) ppm: 5.51 (1H, m), 4.69 (1H, m), 4.15—4.31 (2H, m), 3.76—3.96 (3H, m), 3.68 (1H, m), 3.32—3.38 (2H, m), 3.13 (1H, m), 2.84 (1H, m), 2.76 (3H, s), 2.71 (1H, m), 2.36 (1H, dd, J=14.3, 10.6 Hz), 2.24 (1H, m).

A Mixture of Methyl 5-Cyano-8,11-dioxo-7-hydroxymethyl-9-methoxy-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]-isoquinoline-2-carboxylate and the 10-Methoxy Isomer 30 $Cu(OAc)_2 \cdot H_2O$ (54 mg, 0.27 mmol) and NEt_3 (0.019 ml, 0.135 mmol) were added to a solution of **5** (100 mg, 0.27 mmol) in MeOH (5 ml), and the mixture was stirred for 4 d in an atmosphere of oxygen. Acetate buffer (pH 4.0) was added followed by evaporation of the MeOH. The resultant solution was extracted with AcOEt twice and the combined extracts were washed with brine, dried, and then concentrated. Purification by chromatography (SiO_2 15 ml, *n*-hexane:AcOEt=2:1—1:1) gave **30** (43.5 mg, 40.2%). ^{1}H-NMR ($CDCl_3$) ppm: 5.93 and 5.90 (1H, s), 4.03 (1H, d, J=2.8 Hz), 3.96 (1H, br), 3.831 and 3.825 (3H, s), 3.81 (1H, m), 3.74 and 3.73 (3H, s), 3.67 (1H, m), 3.52 (1H, m), 3.50 (1H, br s), 3.02 (1H, dd, J=9.4, 5.7 Hz), 2.93 (1H, ddd, J=10.9, 2.9, 1.5 Hz), 2.81 (1H, m), 2.68 (1H, m), 2.34 (3H, s), 2.10 (1H, m), 1.93 (1H, dd, J=13.6, 9.6 Hz). ^{13}C-NMR ($CDCl_3$): 185.5. 185.0, 180.3, 180.2, 175.4, 158.8, 158.5, 142.3, 139.4, 139.2, 136.8, 116.8, 107.8, 107.0, 69.9, 69.8, 64.5, 63.8, 62.9, 57.9, 57.5, 56.73, 56.67, 56.4, 56.2, 56.1, 52.4, 42.7, 41.8, 28.9, 25.2, 24.8. SIMS (m/z): 404 $(M+3)^+$, 377 $(M+3-HCN)^+$, 372.

A Mixture of Diphenylmethyl 5-Cyano-8,11-dioxo-7-hydroxymethyl-9-methoxy-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino-[1,2-*b*]isoquinoline-2-carboxylate and the 10-Methoxy Isomer 31 In the same manner as described for **30**, **6** (600 mg) gave **31** (356 mg, 56.1%) along with recovered **6** (133 mg, 22.1%). ^{1}H-NMR ($CDCl_3$) ppm: 7.23—7.43 (10H, m), 6.88 (1H, s), 5.89 (0.6H, s), 5.85 (0.4H, s), 3.87—4.03 (2H, m), 3.79 (3H, s), 3.70 (2H, m), 3.50 (1H, br s), 3.45 (1H, m), 3.15 (1H, dd, J=9, 6 Hz), 2.50—3.00 (3H, m), 2.13—2.33 (1H, m), 2.13 (3H, s), 1.93 (1H, m). SIMS (m/z): 556 $(M+3)^+$, 529 $(M+3-HCN)^+$. IR (KBr): 3500, 2950, 1727, 1676, 1656, 1636, 1610, 1494, 1455, 1355, 1228, 1172, 1059, 1018 cm^{-1}.

A Mixture of 5-Cyano-8,11-dioxo-7-hydroxymethyl-9-methoxy-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylic Acid and the 10-Methoxy Isomer 32 In the same manner as described for **17**, **31** (300 mg) afforded **32** (147 mg, 70.0%). ^{1}H-NMR (D_2O) ppm: 6.02 (0.6H, s), 5.99 (0.4H, s), 4.73 (1H, d, J=2.9 Hz), 4.36 (1H, m), 4.23 (1H, br s), 3.94 (1H, m), 3.82 (1H, m), 3.80 (3H, s), 3.63 (1H, dd, J=12.1, 3.8 Hz), 3.36 (1H, dd, J=10.4, 5.5 Hz), 3.14 (1H, br d, J=10.7 Hz), 2.86 (1H, m), 2.79 (3H, s), 2.72 (1H, m), 2.38 (1H, dd, J=14.4, 10.6 Hz), 2.24 (1H, m). ^{13}C-NMR (D_2O) ppm: 187.1, 181.7, 179.5, 159.7, 159.5, 142.9, 137.1, 116.4, 107.6, 71.0, 66.0, 65.8, 63.0, 57.4, 56.0, 55.0, 42.6, 41.0, 29.3, 24.7, 24.3. SIMS (m/z): 390 $(M+3)^+$, 363 $(M+3-HCN)^+$.

A Mixture of Diphenylmethyl 9-Azido-5-cyano-8,11-dioxo-7-hydroxymethyl-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylate and the 10-Azido Isomer 33 A solution of **6** (250 mg) in CH_3CN (8 ml) and pH 4.0 acetate buffer (8 ml) was treated with NaN_3 (94 mg). The mixture was stirred for 1.5 h, then Fremy's salt (500 mg) was added portionwise during 3 h. The precipitate was collected by filtration, washed with H_2O then dried to give **33** (183 mg, 68.0%) as an orange solid. mp 155—160 °C (dec.). ^{1}H-NMR ($CDCl_3$) ppm: 7.20—7.47 (10H, m), 6.88 (1H, s), 6.23 (1H, s), 3.98 (2H, m), 3.77 (2H, m), 3.51 (1H, br s), 3.47 (1H, m), 2.5—3.3 (4H, m), 2.10—2.35 (1H, m), 2.13 (3H, s), 1.93 (1H, m). SIMS (m/z): 567 $(M+3)^+$. IR (KBr): 3450, 2110, 1726, 1657, 1636, 1596 cm^{-1}.

A Mixture of 9-Azido-5-cyano-8,11-dioxo-7-hydroxymethyl-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylic Acid and the 10-Azido Isomer 34 In the same manner as described for **17**, **33** (250 mg) yielded **34** (114 mg, 64.5%) as a light brown solid. mp 167—170 °C (dec.). ^{1}H-NMR (D_2O) ppm: 6.57 (0.3H, br s), 6.39 (0.7H, br s), 4.41 (1H, m), 4.28 (1H, br s), 4.00 (1H, m), 3.87 (1H, dd, J=12.0, 2.3 Hz), 3.68 (1H, dd, J=12.1, 3.9 Hz), 3.41 (1H, dd, J=10.5, 5.6 Hz), 3.18 (1H, br d, J=8.7 Hz), 2.81—2.93 (1H, m), 2.83 (3H, s), 2.75 (1H, m), 2.43 (1H, dd, J=14.5, 10.7 Hz). ^{13}C-NMR (D_2O) ppm: 185.8, 181.2, 179.2, 147.1, 146.5, 143.3, 138.0, 116.3, 105.8, 71.0, 66.0, 63.2, 57.5, 56.0, 55.0, 42.4, 41.0, 29.2, 24.6. SIMS (m/z): 401 $(M+3)^+$. IR (KBr): 3430, 2118, 1708, 1653, 1635, 1595, 1360, 1257 cm^{-1}.

A Mixture of Diphenylmethyl 9-Amino-5-cyano-8,11-dioxo-7-hydroxymethyl-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino-[1,2-*b*]isoquinoline-2-carboxylate and the 10-Amino Isomer 35 A solution of **33** (850 mg) in a mixture of dioxane (6 ml), CH_3CN (5 ml) and MeOH (15 ml) containing 10% Pd–C (250 mg) was stirred in a stream of H_2 for 4 h 20 min. The catalyst was filtered off, then CH_3CN (10 ml) and H_2O (10 ml) were added to the filtrate. Next, Fremy's salt (780 mg) was added portionwise over 2 h under stirring. After addition of H_2O and NaCl, the mixture was extracted with AcOEt twice. The combined extracts were washed with brine, dried and concentrated. The residue was subjected to chromatography (SiO_2 90 ml, $CHCl_3$:MeOH=1:0—100:1) to give **35** (606 mg, 74.7%) as a red-purple solid. ^{1}H-NMR ($CDCl_3$) ppm: 7.22—7.48 (10H, m), 7.00 (2H, br), 6.82 (1H, s), 5.81 (0.7H, s), 5.72 (0.3H, s), 3.96 (2H, m), 3.67 (2H, m), 3.49 (1H, br s), 3.42 (1H, m), 2.32—3.31 (4H, m), 2.21 (1H, m), 2.15 (3H, s), 1.96 (1H, m). SIMS (m/z): 541 $(M+3)^+$, 514 $(M+3-HCN)^+$. IR (KBr): 3458, 3364, 2950, 1726, 1675, 1652, 1605, 1494, 1454, 1419, 1347, 1256, 1173 cm^{-1}.

A Mixture of 9-Amino-5-cyano-8,11-dioxo-7-hydroxymethyl-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylic Acid and the 10-Amino Isomer 36 In the same manner as described for **17**, **35** (125 mg) gave **36** (23.8 mg, 27.5%) as a red purple solid. mp 150—155 °C (dec.). ^{1}H-NMR (DMSO-d_6) ppm: (major isomer) 6.95 (2H, br), 5.53 (1H, s), 4.29 (1H, d, J=2.7 Hz), 3.64 (1H, dd, J=11.1, 1.9 Hz), 3.62 (1H, m), 3H overlapped with H_2O peak (3.39), 3.11 (1H, dd, J=9.4, 5.7 Hz), 2.60—2.63 (2H, m), 2.40 (1H, ddd, J=12.7, 6.4, 6.3 Hz), 2.22 (3H, s), 1.98 (1H, ddd, J=18.1, 11.3, 2.6 Hz), 1.90 (1H, dd, J=12.9, 9.7 Hz). SIMS (m/z): 375 $(M+3)^+$. IR (KBr): 3430, 1675, 1653, 1626, 1599, 1370, 1340, 1258 cm^{-1}.

9,10-Bis-methylthio-5-cyano-8,11-dioxo-7-hydroxymethyl-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylic Acid 37 A 15% solution of CH_3SNa in H_2O (4.5 ml) was added to a solution of **4** (3.0 g, 8.4 mmol) in CH_3CN (80 ml) and 0.2 M acetate buffer (pH 4.0, 80 ml), and the mixture was stirred for 1 h. Fremy's salt (4.5 g, 16.8 mmol) and H_2O (140 ml) were then added. After 40 min, acetate buffer (20 ml) and a 15% solution of CH_3SNa (3.0 ml) were added and stirring was continued for 50 min. More Fremy's salt (4.3 g) and H_2O were added, then the mixture was stirred for a further 1 h. Excess CH_3SH and CH_3CN were distilled off *in vacuo* and the resultant solution was extracted with AcOEt twice. The combined extracts were washed with brine, dried, and then concentrated. The residue was subjected to chromatography (SiO_2 450 ml, $CHCl_3$:MeOH=1:0—20:1) to give **37** (3.22 g, 85.5%) as a red solid. mp 150—151 °C. *Anal.* Calcd for $C_{20}H_{23}N_3O_5S_2$: C, 53.43; H, 5.17; N, 9.35. Found: C, 53.20; H, 5.24; N, 8.96. ^{1}H-NMR ($CDCl_3$–CD_3OD) ppm: 4.05 (1H, d, J=2.7 Hz), 3.95 (1H, m), 3.79 (1H, dd, J=11.7, 2.8 Hz), 3.65 (1H, dd, J=11.7, 3.3 Hz), 3.53 (1H, br s), 3.52 (1H, m), 3.05 (1H, dd, J=9.6, 5.8 Hz), 2.91 (1H, br d, J=11.0 Hz), 2.81 (1H, ddd, J=18.0, 3.0, 1.2 Hz), 2.63 (1H, m), 2.63 (3H, s), 2.61 (3H, s), 2.36 (3H, s), 2.12 (1H, ddd, J=18.0, 11.0, 2.8 Hz), 1.95 (1H, dd, J=13.6, 9.7 Hz). ^{13}C-NMR ($CDCl_3$–CD_3OD) ppm: 178.9, 178.8, 177.3, 145.4, 144.9, 142.6, 140.0, 116.9, 69.8, 64.6, 63.2, 58.1, 56.8, 56.1, 42.5, 41.8, 28.7, 25.4, 18.2, 18.1. IR (KBr): 3450, 1711, 1653, 1496, 1419, 1261, 1211, 1174 cm^{-1}. SIMS (m/z): 452 $(M+3)^+$, 425 $(M+3-HCN)^+$.

Methyl 10-Bromo-5-cyano-11-hydroxy-7-hydroxymethyl-8-methoxy-13-methyl-1,2,3,4,5,7,12,12a-octahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylate 38a Br_2/AcOH (1 M, 0.9 ml) was added to a solution of **7a** (200 mg, 0.52 mmol) followed by stirring for 14 h 20 min. The mixture was concentrated and partitioned between aqueous $NaHCO_3$ and AcOEt. The AcOEt layer was separated, washed with brine, dried and evaporated. Purification by chromatography (SiO_2 20 ml, *n*-hexane:AcOEt=2:1—1:1) yielded **38a** (54.9 mg, 22.8%). ^{1}H-NMR ($CDCl_3$–CD_3OD) ppm: 6.87 (1H, s), 4.23 (1H, d, J=3 Hz), 4.17 (1H, m), 3.97 (3H, s), 3.80 (3H, s), 3.63—3.83 (2H, m), 3.50 (2H, m), 3.25 (1H, dd, J=9, 6 Hz), 2.47—3.17 (4H, m), 2.33 (3H, s), 2.10 (1H, dd, J=14, 9 Hz). SIMS (m/z): 466, 468 $(M+1)^+$, 439, 441 $(M+1-HCN)^+$.

Sodium 10-Bromo-5-cyano-11-hydroxy-7-hydroxymethyl-8-methoxy-13-methyl-1,2,3,4,5,7,12,12a-octahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylate 38b A 1 N NaOH solution (1.7 ml) was added to a suspension of **38a** (154 mg, 0.33 mmol) in a mixture of MeOH (6 ml) and H_2O (3 ml) followed by stirring for 22 h. After concentration, the residue was subjected to chromatography (Diaion HP-20 20 ml, H_2O : MeOH = 1 : 0—4 : 1) to give **38b** (152 mg, 97.9%). ^{1}H-NMR (CD_3OD) ppm: 6.95 (1H, s), 4.24 (1H, d, J=3 Hz), 4.12 (1H, m), 3.89 (3H, s), 3.60—3.78 (2H, m), 3.58 (1H, m), 3.54 (1H, br s), 3.15 (1H, dd, J=9, 6 Hz), 2.45—3.10 (4H, m), 2.25 (3H, s), 2.06 (1H, dd, J=13, 9 Hz). SIMS (m/z): 474, 476 $(M+1)^+$, 452, 454, 425, 427, 321.

Methyl 5-Cyano-8,8-dimethoxy-7-hydroxymethyl-13-methyl-11-oxo-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylate 39a $Tl(NO_3)_3$ (250 mg, 0.56 mmol) was added to a mixture of **7a** (198 mg, 0.51 mmol) and $CH(OMe)_3$ (4 ml) in MeOH (6 ml) and THF (4 ml) under ice-cooling. The mixture was stirred for 3 h at 0 °C. After addition of H_2O, MeOH and THF were distilled off. The resultant slurry was extracted with AcOEt twice. The combined extracts were washed with brine, dried and concentrated. Purification by chromatography (SiO_2 20 ml, $CHCl_3$: MeOH = 1 : 0—100 : 1) afforded **39a** (160 mg, 75.0%) as a pale brown solid. mp 88—90 °C. *Anal.* Calcd for $C_{21}H_{27}N_3O_6 \cdot 0.2H_2O$: C, 59.90; H, 6.56; N, 9.98. Found: C, 59.87; H, 6.63; N, 9.74. ^{1}H-NMR ($CDCl_3$) ppm: 6.86 (1H, d, J=11 Hz), 6.44 (1H, d, J=11 Hz), 3.89 (1H, d, J=3 Hz), 3.80 (3H, m), 3.72 (3H, s), 3.40—3.56 (2H, m), 3.40 (3H, s), 3.24 (3H, s), 3.08 (1H, m), 2.52—2.92 (3H, m), 2.34 (3H, s), 1.94 (2H, m). SIMS (m/z): 418 $(M+1)^+$, 391 $(M+1-HCN)^+$, 388, 386, 356. IR (KBr): 3510, 2954, 1728, 1674, 1647, 1622, 1460, 1436, 1361, 1331, 1292, 1274, 1207, 1178, 1142, 1060 cm^{-1}.

Sodium 5-Cyano-8,8-dimethoxy-7-hydroxymethyl-13-methyl-11-oxo-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylate 39b In a similar manner to that described for **39a**, **7b** (100 mg) provided **39b** (80.1 mg, 74.4%) as a pale brown solid. mp 182—185 °C (dec.). *Anal.* Calcd for $C_{20}H_{24}N_3NaO_6 \cdot 2H_2O$: C, 52.06; H, 6.12; N, 9.11. Found: C, 52.20; H, 5.93; N, 9.01. ^{1}H-NMR (D_2O) ppm: 7.00 (1H, d, J=10.3 Hz), 6.55 (1H, d, J=10.3 Hz), 4.20 (1H, d, J=2.9 Hz), 3.85 (2H, m), 3.60 (1H, m), 3.58 (1H, m), 3.50 (1H, br s), 3.34 (3H, s), 3.24 (3H, s), 3.04 (1H, dd, J=9.9, 5.5 Hz), 2.72 (1H, dd, J=16.2, 2.6 Hz), 2.70 (1H, m), 2.51 (1H, m), 2.21 (3H, s), 2.03 (1H, m), 2.01 (1H, dd, J=13.3, 9.9 Hz). ^{13}C-NMR (D_2O) ppm: 185.8, 184.1, 147.2, 146.2, 139.8, 132.3, 119.2, 96.4, 70.3, 64.9, 63.3, 59.2, 57.8, 57.8, 52.1, 51.9, 45.3, 41.9, 30.1, 25.3. SIMS (m/z): (free carboxylic acid) 404 $(M+1)^+$. IR (KBr): 3420, 1674, 1647, 1622, 1556, 1460, 1395, 1210, 1140, 1065 cm^{-1}.

Sodium 10-Bromo-5-cyano-8,8-dimethoxy-7-hydroxymethyl-13-methyl-11-oxo-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylate 40 In a similar manner to that described for **39a**, **38b** (100 mg) gave **40** (73.0 mg, 68.7%). ^{1}H-NMR (D_2O) ppm: 7.59 (1H, s), 4.21 (1H, d, J=2.9 Hz), 3.85 (2H, m), 3.60 (2H, m), 3.51 (1H, br s), 3.39 (3H, s), 3.28 (3H, s), 3.05 (1H, dd, J=9.9, 5.5 Hz), 2.78 (1H, dd, J=15.8, 2.5 Hz), 2.73 (1H, br d, J=11.3 Hz), 2.52 (1H, m), 2.22 (3H, s), 2.10 (1H, m), 2.02 (1H, dd, J=13.5, 10.0 Hz). ^{13}C-NMR (D_2O) ppm: 184.1, 179.0, 147.4, 146.9, 138.7, 126.8, 119.1, 97.9, 70.2, 64.9, 63.2, 59.3, 57.7, 57.7, 52.3, 52.0, 45.3, 41.9, 30.0, 26.3.

Diphenylmethyl 5-Cyano-7-hydroxymethyl-11-methoxyimino-13-methyl-8-oxo-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylate 41 $H_2NOCH_3 \cdot HCl$ (79 mg, 0.95 mmol) was added to a solution of **6** (100 mg, 0.19 mmol) in MeOH (3 ml), followed by stirring for 5 h. The reaction mixture was concentrated and partitioned between AcOEt and pH 7.7 phosphate buffer. The AcOEt layer was separated, washed with brine, dried and evaporated. The residue was chromatographed (SiO_2 10 ml, $CHCl_3$) to give **41** (89.6 mg, 84.9%) as a light brown solid. mp 77—78 °C. ^{1}H-NMR ($CDCl_3$) ppm: 7.57 (1H, d, J=11 Hz), 7.35 (10H, m), 6.88 (1H, s), 6.37 (1H, d, J=11 Hz), 4.20 (3H, s), 4.05 (1H, d, J=3 Hz), 3.98 (1H, m), 3.72 (1H, m), 3.50 (1H, br s), 3.47 (1H, m), 2.90—3.33 (3H, m), 2.23—2.83 (3H, m), 2.14 (3H, s), 1.97 (1H, dd, J=13, 9 Hz). SIMS (m/z): 555 $(M+3)^+$, 525. IR (KBr): 3450, 2940, 1727, 1639, 1624, 1515, 1494, 1456, 1349, 1291, 1275, 1170, 1052 cm^{-1}.

5-Cyano-7-hydroxymethyl-11-methoxyimino-13-methyl-8-oxo-1,2,3,4,-5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylic Acid 42 In the same manner as described for **17**, **41** (724 mg) provided **42** (398 mg, 78.6%) as a pale yellow lyophilized solid. mp 150—155 °C (dec.). *Anal.* Calcd for $C_{19}H_{22}N_4O_5 \cdot H_2O$: C, 56.43; H, 5.98; N, 13.85. Found: C, 56.72; H, 5.91; N, 13.49. ^{1}H-NMR (CD_3OD) ppm: 7.67 (1H, d, J=10.2 Hz), 6.39 (1H, d, J=10.2 Hz), 4.26 (1H, d, J=2.8 Hz), 4.20 (3H, s), 3.87 (1H, m), 3.74 (1H, dd, J=11.3, 2.4 Hz), 3.56 (1H, dd, J=11.3, 4.3 Hz), 3.52 (1H, m), 3.50 (1H, br s), 3.25 (1H, dd, J=9.6, 5.6 Hz), 3.03 (1H, dd, J=16.8, 2.3 Hz), 2.83 (1H, br d, J=9.6 Hz), 2.60 (1H, m), 2.33 (3H, s), 2.32 (1H, m), 2.05 (1H, dd, J=13.4, 9.7 Hz). ^{13}C-NMR (CD_3OD) ppm: 186.4, 179.0, 148.7, 144.5, 133.4, 132.3, 125.5, 118.7, 71.6, 66.1, 64.9, 64.6, 59.1, 58.7, 57.7, 43.6, 42.2, 29.5, 27.1. SIMS (m/z): 387 $(M+1)^+$, 360 $(M+1-HCN)^+$. IR (KBr): 3420, 2948, 1715, 1639, 1512, 1459, 1420, 1365, 1208, 1053 cm^{-1}.

Diphenylmethyl 5-Cyano-11-hydroxyimino-7-hydroxymethyl-13-methyl-8-oxo-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylate 43 In a similar manner to that described for **41**, except that $H_2NOH \cdot HCl$ was used in place of $H_2NOMe \cdot HCl$, **6** (100 mg) gave **43** (58.2 mg, 55%). ^{1}H-NMR ($CDCl_3$–CD_3OD) ppm: 7.70 (1H, d, J=11 Hz), 7.30 (10H, m), 6.85 (1H, s), 6.30 (1H, d, J=11 Hz), 4.15 (1H, d, J=3 Hz), 3.95 (1H, m), 3.40—3.77 (4H, m), 2.83—3.30 (3H, m), 2.43—2.73 (1H, m), 2.10 (3H, s), 1.93—2.33 (2H, m). SIMS (m/z): 541 $(M+3)^+$, 525.

5-Cyano-11-hydroxyimino-7-hydroxymethyl-13-methyl-8-oxo-1,2,3,4,5,-7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylic Acid 44 In the same manner as described for **17**, **43** (190 mg) yielded **44** (110 mg, 83.9%) as a pale yellow lyophilized solid. mp 148—155 °C (dec.). ^{1}H-NMR (CD_3OD) ppm: 7.79 (1H, d, J=10.2 Hz), 6.38 (1H, d, J=10.2 Hz), 4.27 (1H, d, J=2.8 Hz), 3.88 (1H, m), 3.74 (1H, dd, J=11.3, 2.3 Hz), 3.57 (1H, dd, J=11.3, 4.4 Hz), 3.52 (1H, m), 3.49 (1H, br s), 3.26 (1H, dd, J=9.6, 5.7 Hz), 3.08 (1H, dd, J=16.8, 2.4 Hz), 2.83 (1H, br d, J=11.3 Hz), 2.60 (1H, m), 2.34 (1H, m), 2.33 (3H, s), 2.06 (1H, dd, J=13.3, 9.7 Hz). ^{13}C-NMR (CD_3OD) ppm: 186.7, 179.2, 149.2, 145.5, 132.6, 131.2, 125.3, 118.7, 71.6, 66.1, 64.7, 59.1, 58.7, 57.7, 43.6, 42.1, 29.5, 27.2. SIMS (m/z): 373 $(M+1)^+$, 346 $(M+1-HCN)^+$. IR (KBr): 3430, 1639, 1426, 1363 cm^{-1}.

Diphenylmethyl 5-Cyano-8,11-dioxo-9,10-epoxy-7-hydroxymethyl-13-methyl-1,2,3,4,5,7,8,9,10,11,12,12a-dodecahydro-1,4-iminoazepino[1,2-*b*]-isoquinoline-2-carboxylate 45 Aqueous NaOCl (6.0 ml) was added portionwise to a solution of **6** (1.0 g, 1.91 mmol) in dioxane (24 ml) during 6 h under stirring. After addition of H_2O and NaCl, the mixture was extracted with AcOEt twice. The combined extracts were washed with brine, dried and evaporated. Purification of the residue by chromatography (SiO_2 100 ml, n-hexane : AcOEt = 3 : 1—3 : 2) gave **45** (504 mg, 48.9%) as a pale orange solid (stereoisomeric mixture at C-8 and C-9). mp 108—113 °C (dec.). *Anal.* Calcd for $C_{31}H_{29}N_3O_6 \cdot H_2O$: C, 66.78; H, 5.60; N, 7.54. Found: C, 66.39; H, 5.46; N, 7.16. ^{13}C-NMR ($CDCl_3$) ppm: 190.4, 189.5, 173.7, 140.6, 139.7, 128.7, 128.24, 128.15, 127.1, 127.0, 116.5, 77.8, 69.8, 64.5, 62.4, 57.7, 56.8, 56.1, 54.0, 53.5, 43.0, 41.6, 28.7, 25.0. SIMS (m/z): 542 $(M+3)^+$, 515 $(M+3-HCN)^+$. IR (KBr): 3450, 2952, 1727, 1686, 1632, 1495, 1455, 1371, 1293, 1171 cm^{-1}.

5-Cyano-8,11-dioxo-9,10-epoxy-7-hydroxymethyl-13-methyl-1,2,3,4,-5,7,8,9,10,11,12,12a-dodecahydro-1,4-imino-azepino[1,2-*b*]isoquinoline-2-carboxylic Acid 46 In the same manner as described for **17**, **45** (110 mg) yielded **46** (65.8 mg, 86.4%) as a pale orange solid. The physicochemical properties of **46** (stereoisomeric mixture at C-9 and C-10) were as follows. ^{1}H-NMR data are those for the major isomer only. mp 138—142 °C (dec.). ^{1}H-NMR (CD_3OD) ppm: (major isomer) 4.55 (1H, d, J=2.7 Hz), 3.98 (1H, m), 3.91 (1H, d, J=4.0 Hz), 3.89 (1H, m), 3.88 (1H, d, J=4.0 Hz), 3.82 (1H, br s), 3.71 (1H, dd, J=11.5, 2.9 Hz), 3.53 (1H, dd, J=11.5, 4.8 Hz), 3.37 (1H, dd, J=9.8, 5.8 Hz), 2.89 (1H, ddd, J=17.3, 3.2, 1.3 Hz), 2.83 (1H, m), 2.67 (1H, m), 2.55 (3H, s), 2.20 (1H, dd, J=13.8, 10.1 Hz), 2.10 (1H, ddd, J=17.2, 10.6, 2.8 Hz). SIMS (m/z): 376 $(M+3)^+$, 374 $(M+1)^+$. IR (KBr): 3430, 1688, 1638, 1374, 1297, 1202, 1136 cm^{-1}.

Diphenylmethyl 9 (or 10)-Anilino-5-cyano-8,11-dioxo-10 (or 9)-hydroxy-7-hydroxymethyl-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylate 47 and Diphenylmethyl 10(or 9)-Anilino-5-cyano-8,11-dioxo-9(or 10)-hydroxy-7-hydroxymethyl-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylate 48 Aniline (0.13 ml) was added portionwise over 8.5 h to a solution of **45** (150 mg, 0.28 mmol) in EtOH (7 ml) at 40—50 °C. The mixture was concentrated, followed by chromatographic purification (SiO_2 20 ml, n-hexane : AcOEt = 3 : 1—2 : 1) to provide **47** (45.7 mg, 26.0%) and **48** (23.5 mg, 13.4%), each as a dark blue solid. **47**: mp 144—145 °C. *Anal.* Calcd for $C_{37}H_{34}N_4O_6 \cdot H_2O$: C, 68.67; H, 5.78; N, 8.45. Found: C, 69.03; H, 5.54; N, 8.68. ^{1}H-NMR ($CDCl_3$) ppm: 7.27—7.42 (12H, m), 7.04 (1H, m), 6.93 (2H, m), 6.90 (1H, s), 6.63 (1H, br s), 4.00 (1H, d, J=2.8 Hz), 3.96 (1H, m), 3.83 (1H, dd, J=11.7, 3.1 Hz), 3.73 (1H, dd, J=11.7, 2.8 Hz), 3.51 (1H, br s), 3.48 (1H, m), 3.11 (1H, dd, J=9.5, 5.8 Hz), 2.95 (1H, br d, J=9.6 Hz), 2.81 (1H, ddd, J=18.1, 3.0, 1.4 Hz), 2.16 (1H, ddd, J=17.9, 11.1, 3.1 Hz), 2.15 (3H, s), 1.94 (1H, dd, J=13.6, 9.7 Hz). IR (KBr): 3362, 1731, 1684, 1643, 1596, 1521, 1496, 1445, 1309, 1169 cm^{-1}. SIMS (m/z): 633 $(M+3)^+$, 606 $(M+3-HCN)^+$. **48**; IR (KBr): 3450, 1730, 1682, 1640, 1595, 1520, 1488, 1437, 1310, 1165 cm^{-1}. SIMS (m/z): 633 $(M+3)^+$, 606 $(M+3-HCN)^+$.

Diphenylmethyl 9(or 10)-Anilino-5-cyano-8,11-dioxo-7-hydroxymethyl-10(or 9)-methoxy-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino[1,2-*b*]isoquinoline-2-carboxylate 49 In the same manner as described for **15**, **47** (100 mg) gave **49** (52.8 mg, 51.7%) as a purple solid. mp 117—118 °C. *Anal.* Calcd for $C_{38}H_{36}N_4O_6 \cdot 0.5H_2O$: C, 69.81; H, 5.70; N, 8.57. Found: C, 69.45; H, 5.68; N, 8.83. ^{1}H-NMR ($CDCl_3$) ppm: 7.28—7.38 (12H, m), 7.11 (1H, t, J=7.4 Hz), 7.03 (2H, d, J=7.5 Hz), 6.91 (1H, s), 6.89 (1H, br s), 4.01 (1H, m), 3.99 (1H, d, J=3.0 Hz), 3.84 (1H, dd, J=11.6, 3.3 Hz), 3.73 (1H, m), 3.52 (1H, br s), 3.50 (1H, dd, J=6.3, 2.2 Hz), 3.38 (3H, s), 3.11 (1H, dd, J=9.5, 5.8 Hz), 2.97 (1H, m), 2.81 (1H, ddd, J=17.7, 3.2, 1.4 Hz), 2.69 (1H, ddd, J=13.4, 6.3, 6.2 Hz), 2.17 (3H, s), 2.16 (1H, ddd, J=17.7, 11.1, 3.0 Hz), 1.95 (1H, dd, J=13.6, 9.6 Hz). SIMS (m/z): 647 $(M+3)^+$, 620 $(M+3-HCN)^+$. IR (KBr): 3470, 3346, 2948, 1728, 1654, 1591, 1507, 1496, 1445, 1310, 1273, 1228, 1170 cm^{-1}.

Sodium 9(or 10)-Anilino-5-cyano-8,11-dioxo-7-hydroxymethyl-10(or 9)-methoxy-13-methyl-1,2,3,4,5,7,8,11,12,12a-decahydro-1,4-iminoazepino-[1,2-*b*]isoquinoline-2-carboxylate 50 In the same manner as described for **17**, **49** (120 mg) afforded **50** (124 mg, 66.8%) as a purple solid. mp 130—135 °C (dec.). *Anal.* Calcd for $C_{25}H_{25}N_4NaO_6 \cdot 3H_2O$: C, 54.15; H, 5.63; N, 10.10. Found: C, 54.42; H, 5.31; N, 10.06. ^{1}H-NMR (DMSO-d_6) ppm: 8.27 (1H, s), 7.23 (2H, m), 6.99 (3H, m), 4.30 (1H, d, J=2.7 Hz), 3.69 (2H, m), 3.35—3.53 (3H, m), 3.39 (1H, s), 3.33 (3H, s), 3.10 (1H, dd, J=9.3, 5.8 Hz), 2.66 (1H, br d, J=9.4 Hz), 2.58 (1H, dd, J=17.1, 1.9 Hz), 2.39 (1H, m), 2.21 (3H, s), 2.03 (1H, ddd, J=17.1, 11.0, 2.0 Hz), 1.89 (1H, dd, J=12.8, 9.7 Hz). SIMS (m/z): 481 $(M+3)^+$, 454 $(M+3-HCN)^+$. IR (KBr): 3400, 1653, 1633, 1587, 1507, 1445, 1389, 1312, 1259 cm^{-1}.

Evaluation of Antitumor Activity HeLa S_3 cells (5×10^4) were seeded in plastic tubes or dishes containing 1 ml of growth medium. Graded concentrations of drugs were added 24 h after the cells had been seeded. After 72 h of drug exposure, the tumor cells were counted and the IC_{50} value was determined.

P388 cells (1×10^6) were implanted intraperitoneally (ip) into $CD2F_1$ mice and ip administration of drugs was started the day after tumor implantation. Antitumor efficacy was expressed in terms of increase of life span (ILS).

Acknowledgment We are grateful to Mrs. M. Yoshida and her staff for detailed NMR studies of analogues.

References and Notes

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