SYNTHESIS OF AMINOBENZO[*b*]PYRROLIZINONE AND AMINOBENZO[*b*]INDOLIZINONE DERIVATIVES †

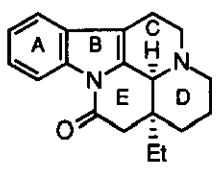
Masanao Taga, Hisao Ohtsuka, Isao Inoue, Takayuki Kawaguchi, Sumihiro Nomura, Koichiro Yamada, Tadamasa Date, Hajime Hiramatsu, and Yasuhiko Sato*

Organic Chemistry Research Laboratory, Tanabe Seiyaku Co., Ltd. 2-2-50, Kawagishi, Toda-shi, Saitama 335, Japan

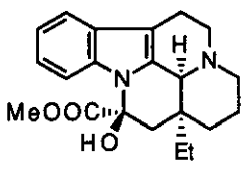
Abstract — The fused tricyclic indole derivatives (**4a and 4b-1~4b-7**) possessing an amino function on the benzo[*b*]pyrrolizinone or the benzo[*b*]-indolizinone skeleton were synthesized *via* intramolecular reductive cyclization and Curtius rearrangement, and these compounds exhibited anti-anoxia activity.

There are many naturally occurring fused indole derivatives which show important pharmacological activities.[1] For example, indole alkaloids such as eburunamonine (**1**) and vincamine (**2**) are known as cerebral vasodilators.[1] Simoji and co-workers reported that the conformationally restricted analogue (**3**) of **1** exhibited antiarrhythmic activity.[2]

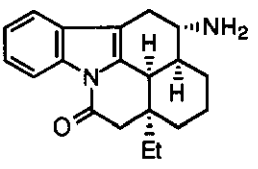
In our search for new drugs similar to **1** in physiological effect, we have prepared the fused tricyclic indole derivatives (**4**) which lacked C- and D-rings on **1**, expecting that these compounds would have a higher



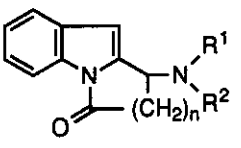
Eburunamonine (**1**)



Vincamine (**2**)



(**3**)

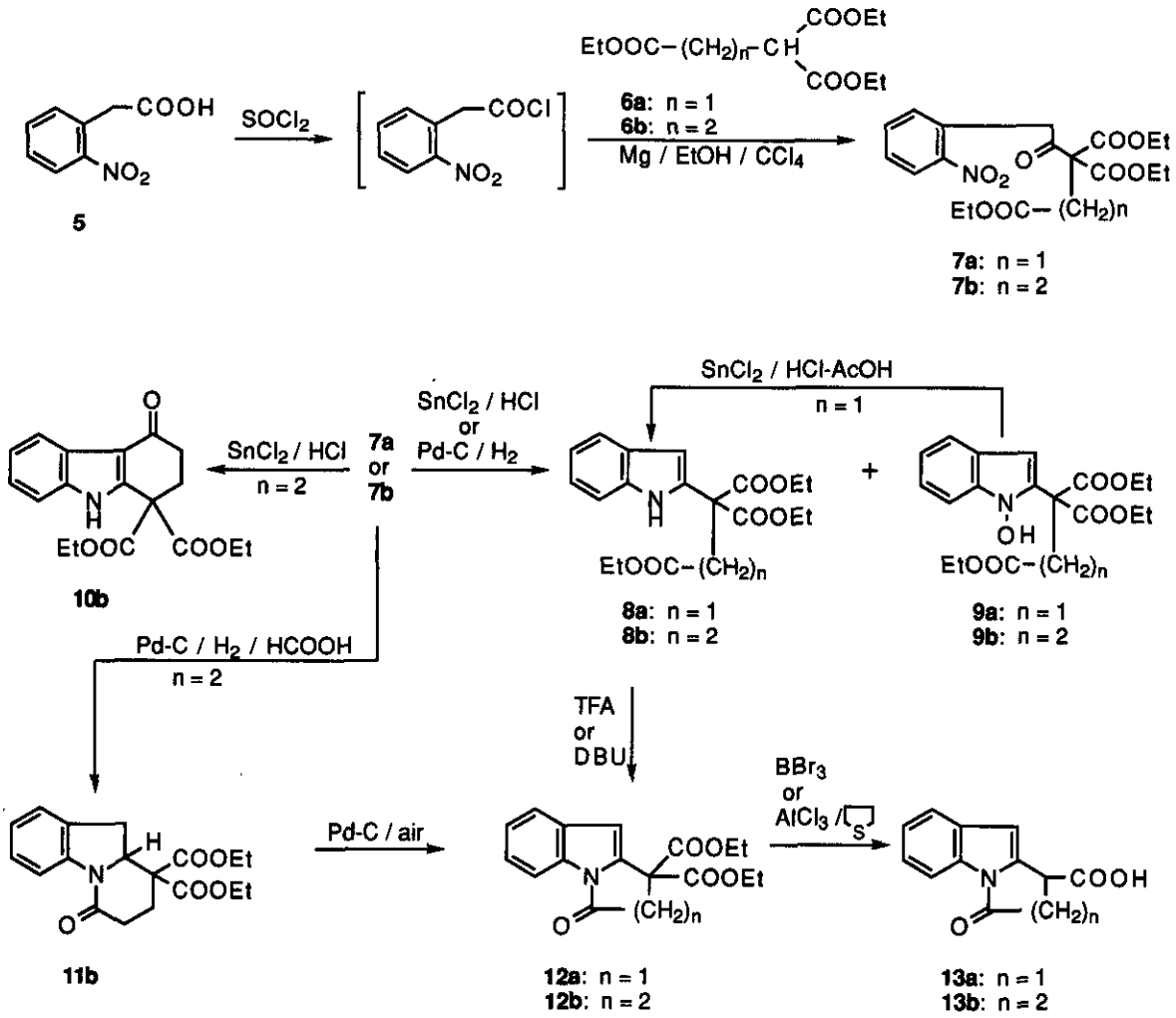


(**4**) n=1, 2

†Dedicated to the memory of Emeritus Professor Yoshio Ban (Hokkaido University).

hydrophilicity when compared with **1**, and consequently a different distribution in body and different pharmacokinetics. In the present paper, we wish to report the synthesis of the aminobenzo[*b*]pyrrolizinone (**4a**) and aminobenzo[*b*]indolizinone derivatives (**4b-1~4b-7**) that possess anti-anoxia activity.

The tricarboxylates (**7a** and **7b**) were prepared by treatment with the acid chloride of 2-nitrophenylacetic acid (**5**) and the malonate derivatives (**6a** and **6b**) in good yields (89% and 75%). Intramolecular reductive cyclization of **7a** with stannous chloride in a hydrochloric acid-ether solution gave the desired compound (**8a**) in 69% yield. On the other hand, reduction of **7b** in the same reaction conditions gave the carbazolone derivative (**10b**) in 61% yield. Catalytic hydrogenation of **7a** and **7b** over palladium charcoal in a hydrochloric acid-ethanol solution gave the hydroxy indole derivatives (**9a**; 73% and **9b**; 66%) as a major



product accompanied by **8a** and **8b** (18% each). The compound (**9a**) was easily converted to **8a** (70%) with stannous chloride in 1.35 *N* hydrochloric acid in acetic acid. Hydrogenation of **7b** over palladium charcoal in an acetic acid solution gave the desired compound (**8b**) in 85% yield together with a trace of **9b** (1%) and **11b** (7%). When **7b** was reduced in formic acid as a solvent over palladium charcoal under a hydrogen atmosphere, **8b** was obtained in poor yield (44%) and the major product was the over-reduced tricyclic compound (**11b**; 56%). Cyclization of **8a** and **8b** thus obtained with trifluoroacetic acid (TFA) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene gave the benzo[*b*]pyrrolizinone (**12a**; 85%) and the benzo[*b*]indolizinone derivative (**12b**; 82%), respectively. Dehydration of **11b** also afforded **12b** in 20% yield. Decarboxylation of **12a** and **12b** with boron tribromide in dichloromethane, or aluminum chloride in tetrahydrothiophene[3] gave the corresponding carboxylic acids (**13a**; 88% and **13b**; 91%). Esterification of **13a** in acidic ethanol gave the crystalline compound (**14a**; 92%), whose structure was confirmed by X-ray crystallographic analysis as shown in Figure 1.[4]

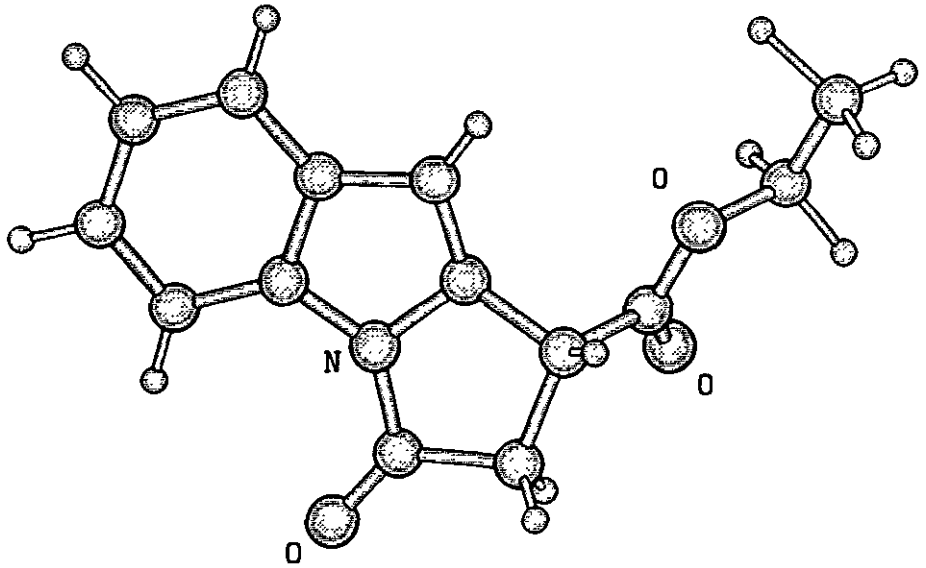
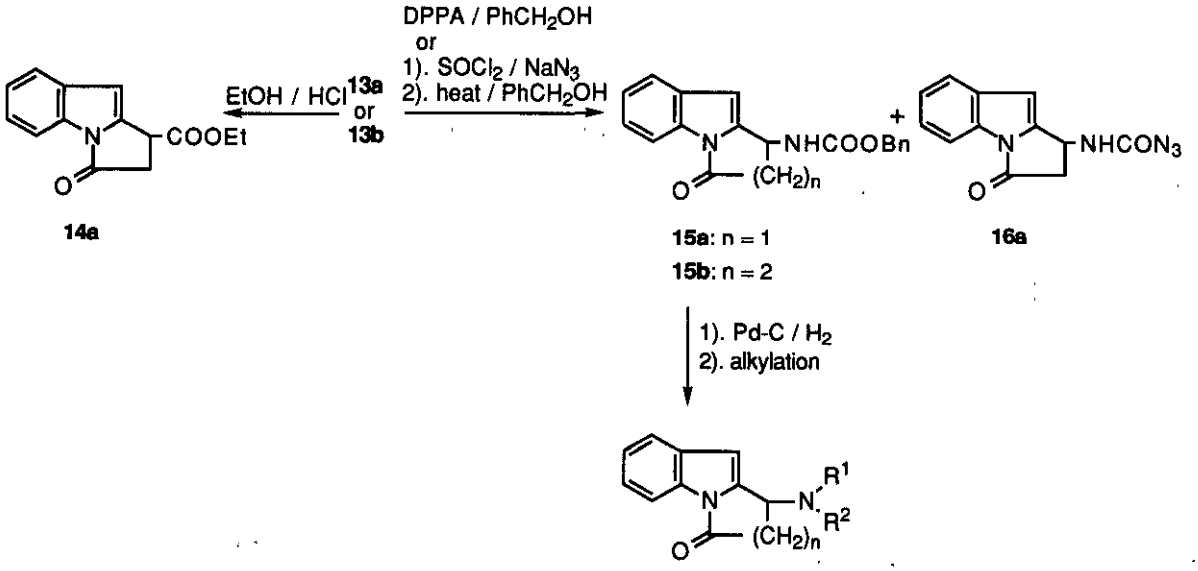


Figure. 1 Parallel View of **14a**

The benzo[*b*]indolizinone carbamate (**15b**) was readily obtained from **13b** in 86% yield by the ordinary Curtius reaction. However, rearrangement of the carboxylic acid on the benzo[*b*]pyrrolizinone ring (**13a**) to the carbamate (**15a**) by Shioiri method[5] was attained with difficulty in 23% yield together with the carbamoyl azide (**16a**; 18%) as a by-product. Removal of the benzyloxycarbonyl groups of **15a** and **15b** by hydrogenation gave the desired amines (**4a**; 90% and **4b-1**; 96%). Reductive arylation/alkylation of **4b-1**



4a: $R^1 = R^2 = H$, n = 1
4b-1: $R^1 = R^2 = H$, n = 2
4b-2: $NR^1R^2 = N = CHPh$, n = 2
4b-3: $R^1 = H$, $R^2 = CH_2Ph$, n = 2
4b-4: $R^1 = H$, $R^2 = Bu^n$, n = 2
4b-5: $R^1 = Me$, $R^2 = CH_2Ph$, n = 2
4b-6: $R^1 = R^2 = Me$, n = 2
4b-7: $R^1 = H$, $R^2 = Me$, n = 2

with benzaldehyde or butyraldehyde gave the corresponding benzylamino (**4b-3**; 75%) and butylamino derivatives (**4b-4**; 69%), respectively. The compounds (**4b-5**; 98% and **4b-6**; 71%) were obtained by the Eschweiler-Clark methylation procedure.[6] Removal of benzyl group of **4b-5** by hydrogenation gave the methylamino derivative (**4b-7**) in 72% yield.

These indole derivatives (**4a and 4b-1~4b-7**) showed potent anti-anoxia activity, and further pharmacological evaluation in detail are now in progress.

Table 1. Physico-chemical data for the compounds (**4a, 4b-1~4b-7, 7a-b, 8a-b, 9a-b, 10b, 11b, 12a-b, 13a-b, 14a, 15a-b and 16a**).

Compounds (Formula)	mp/°C	Elemental analysis % Calcd (Found) C	H	N	Cl	Ir (Nujol) n / cm^{-1} [Ms m/z (M^+)]	^{1}H-Nmr ($CDCl_3$) δ
4a • HCl ($C_{11}H_{10}N_2O$ • HCl)	290-292 (decomp.)	59.33 (59.51	4.98 4.95	12.58 12.77	15.92 16.11)	1745, 3480 [186]	(D_2O-DMSO-d_6): 3.00-3.95 (2H, m), 5.00-5.25 (1H, m), 6.90 (1H, br s), 7.35-7.85 (3H, m), 7.90-8.10 (1H, m)
4b-1 ($C_{12}H_{12}N_2O$)	92-93	71.98 (71.69	6.04 5.96	13.99 13.89	- -)	1700, 3380 [200]	1.60 (2H, s), 1.75-2.50 (2H, m), 2.50-3.20 (2H, m), 4.10-4.30 (1H, m), 6.48 (1H, br s), 7.20-7.60 (3H, m), 8.30-8.50 (1H, m)
4b-2 ($C_{19}H_{16}N_2O$)	143.5-144.5	79.14 (79.08	5.59 5.42	9.72 9.77	- -)	1640, 1700 [288]	2.20-2.50 (2H, m), 2.60-3.40 (2H, m), 4.80 (1H, t, J = 5.3 Hz), 6.38 (1H, s), 7.15-7.50 (6H, m), 7.50-7.80 (2H, m), 8.30-8.55 (2H, m)
4b-3 ($C_{19}H_{18}N_2O$)	99.5-100.5	78.59 (78.71	6.25 6.17	9.65 9.65	- -)	1695, 3300 [290]	1.51 (1H, br s), 1.98-2.36 (2H, m), 2.62-3.21 (2H, m), 3.92 (2H, s), 4.10 (1H, t-like, J = 3.9 Hz), 6.53 (1H, s), 7.20-7.53 (3H, m), 8.44-8.49 (1H, m)
4b-4 • HCl ($C_{16}H_{20}N_2O$ • HCl • 1/3H_2O)	186-188	64.31 (64.63	7.30 7.22	9.38 9.68	11.86 12.15)	1710, 3420 [256]	(DMSO-d_6): 0.91 (3H, t, J = 6.6 Hz), 1.06-3.70 (10H, m), 4.70-4.90 (1H, m), 7.06 (1H, br s), 7.10-7.70 (3H, m), 8.30-8.45 (1H, m), 9.60-9.90 (2H, br s)
4b-5 ($C_{20}H_{20}N_2O$)	115-116	78.92 (79.00	6.62 6.60	9.20 9.31	- -)	1705, 3400 [304]	2.00-3.15 (4H, m), 2.30 (3H, s), 3.70 (2H, ABq, J = 13.4 Hz), 4.00-4.10 (1H, m), 6.60 (1H, d-like), 7.15-7.55 (3H, m), 8.35-8.47 (1H, m)
4b-6 • HCl ($C_{13}H_{14}N_2O$ • HCl)	237-238 (decomp.)	62.27 (62.13	6.03 5.98	11.17 11.36	14.14 13.84)	1710, 3060 [214]	(DMSO-d_6): 2.63 (3H, s), 2.70-3.40 (4H, m), 4.65-4.85 (1H, m), 7.06 (1H, s), 7.20-7.70 (3H, m), 8.30-8.40 (1H, m), 9.96 (2H, br s)
4b-7 • HCl ($C_{14}H_{16}N_2O$ • HCl)	265-267 (decomp.)	63.51 (63.39	6.47 6.46	10.58 10.55	13.39 13.49)	1700 [228]	(DMSO-d_6): 2.70 (6H, s), 2.70-3.25 (2H, m), 3.30-3.50 (2H, m), 4.75-5.00 (1H, br s), 7.23 (1H, s), 7.25-7.50 (2H, m), 7.60-7.72 (1H, m), 8.25-8.40 (1H, m), 11.40-11.80 (1H, br s)

(Table 1. continued)

7a ($C_{19}H_{23}NO_9$)	oil					1610, 1730 [410 (M^++1)]	1.35 (9H, t, J = 6.5 Hz), 3.24 (2H, s), 4.11 (2H, q, J = 6.5 Hz), 4.33 (4H, q, J = 6.4 Hz), 4.71 (2H, s), 7.24-7.70 (3H, m)
7b ($C_{20}H_{25}NO_9$)	oil					1610, 1730 [424 (M^++1)]	1.25 (3H, t, J = 7.0 Hz), 1.33 (6H, t, J = 7.0 Hz), 2.46 (4H, s), 4.09 (2H, q, J = 7.0 Hz), 4.29 (4H, q, J = 7.0 Hz), 4.57 (2H, s), 7.16-7.65 (3H, m), 7.95-8.15 (1H, m)
8a ($C_{19}H_{23}NO_6$)	86.5-87.5	63.14 (63.33	6.42 6.50	3.88 4.01	- -)	1730, 1750, 3390 [361]	1.11 (3H, t, J = 6.8 Hz), 1.23 (6H, t, J = 7.0 Hz), 3.47 (2H, s), 3.87-4.43 (6H, m), 6.35 (1H, br s), 6.95-7.60 (4H, m), 9.55 (1H, br s)
8b ($C_{20}H_{25}NO_6$)	68-69	63.98 (63.80	6.71 6.76	3.73 3.83	- -)	1700, 1720, 3360 [375]	1.17 (3H, t, J = 7.0 Hz), 1.25 (6H, t, J = 6.9 Hz), 2.15-2.40 and 2.60-2.85 (each 2H, m), 4.05 (2H, q, J = 7.0 Hz), 4.25 (4H, q, J = 7.0 Hz), 6.44 (1H, d, J = 2.2 Hz), 7.00-7.60 (4H, m), 9.54 (1H, br s)
9a ($C_{19}H_{23}NO_7$)	oil					1730, 3320 [377]	1.26 (9H, t, J = 7.2 Hz), 3.42 (2H, s), 4.16 (2H, q, J = 7.2 Hz), 4.37 (4H, q, J = 7.2 Hz), 6.27 (1H, s), 7.00-7.60 (4H, m), 8.45 (1H, br s)
9b ($C_{20}H_{25}NO_7$)	oil					1730, 3300 [391]	1.02 (3H, t, J = 6.9 Hz), 1.26 (6H, t, J = 7.4 Hz), 3.85 (2H, q, J = 7.0 Hz), 4.29 (4H, q, J = 7.4 Hz), 6.29 (1H, s), 6.85-7.60 (4H, m), 8.18 (1H, s)
10b ($C_{18}H_{19}NO_5$)	140-142	65.64 (65.83	5.82 5.80	4.25 4.11	- -)	1635, 1735 [329]	1.29 (6H, t, J = 7.0 Hz), 2.76 (4H, s), 4.26 (4H, q, J = 6.9 Hz), 7.10-7.50 (3H, m), 8.15-8.35 (1H, m), 9.57 (1H, br s)
11b ($C_{18}H_{21}NO_5$)	80.5-82	65.24 (65.35	6.39 6.33	4.23 4.23	- -)	1660, 1730 [331]	(400 Mc): 1.05 (3H, t, J = 7.1 Hz), 1.32 (3H, t, J = 7.1 Hz), 2.24 (1H, dt, J = 13.8 and 8.6 Hz), 2.59-2.80 (3H, m), 3.34 (1H, dd, J = 16.5 and 9.5 Hz), 3.66 (1H, dd, J = 16.5 and 9.0 Hz), 4.09 (2H, q, J = 7.1 Hz), 4.29 (2H, q, J = 7.1 Hz), 4.61 (1H, dd, J = 9.0 and 9.5 Hz), 7.17-7.18 and 8.16 (4H, m)

(Table 1. continued)

12a ($C_{17}H_{17}NO_5$)	76-78	64.75 (64.69	5.43 5.44	4.44 4.59	- -)	1745 (br) [315]	1.31 (6H, t, J = 7.1 Hz), 3.68 (2H, s), 4.30 (4H, q, J = 7.1 Hz), 6.60 (1H, s), 7.21-7.65 (3H, m), 7.95-8.15 (1H, m)
12b ($C_{18}H_{19}NO_5$)	53.5-55	65.64 (65.81	5.82 5.85	4.25 4.19	- -)	1690, 1730 [329]	1.30 (6H, t, J = 7.0 Hz), 2.55-3.95 (4H, m), 4.30 (4H, q, J = 7.0 Hz), 6.72 (1H, s), 7.15-7.60 (3H, m), 8.35-8.53 (1H, m)
13a ($C_{12}H_9NO_3$)	196-197 (decomp.)	66.97 (66.90	4.22 4.25	6.51 6.69	- -)	1690, 1730 [215]	3.35 (2H, d, J = 6.6 Hz), 4.46 (1H, t-like, J = 6.5 Hz), 6.58 (1H, d, J = 2.0 Hz), 7.15-7.75 (3H, m), 7.85-8.10 (1H, m)
13b ($C_{13}H_{11}NO_3$)	142-143	68.11 (67.89	4.84 4.72	6.44 6.04	- -)	1660, 1720 [229]	(400 Mc): 2.36 (1H, m), 2.44 (1H, m), 2.80 (1H, ddd, J = 17.7, 6.8 and 4.9 Hz), 3.04 (1H, ddd, J = 17.7, 6.8 and 5.1 Hz), 4.13 (1H, t, J = 5.5 Hz), 6.61 (1H, s), 7.27 and 7.33 (each 1H, m), 7.51 (1H, dd, J = 7.4 and 1.3 Hz), 8.46 (1H, dd, J = 8.2 and 1.2 Hz)
14a ($C_{14}H_{13}NO_3$)	72-73	62.12 (69.10	5.39 5.31	5.76 5.37	- -)	1730 [243]	1.37 (3H, t, J = 7.0 Hz), 3.25-3.50 (2H, m), 4.10-4.45 (1H, m), 4.29 (2H, q, J = 7.0 Hz), 6.51 (1H, s), 7.10-7.70 (3H, m), 7.90-8.30 (1H, m)
15a ($C_{19}H_{16}N_2O_3$)	193-195	71.24 (71.11	5.03 5.00	8.75 8.90	- -)	1685, 1735, 3350 [320]	($CDCl_3$-DMSO-d_6): 3.00-3.40 (2H, m), 5.13 (2H, s), 5.15-5.50 (1H, m), 6.49 (1H, br s), 7.15-7.65 (8H, m), 7.90-8.10 (1H, m)
15b ($C_{20}H_{18}N_2O_3$)	174-175	71.84 (71.60	5.43 5.24	8.38 8.47	- -)	1670, 1710, 3290 [334]	1.80-2.60 (2H, m), 2.70-2.90 (2H, m), 4.90-5.50 (2H, m), 5.15 (2H, s), 6.45 (1H, s), 7.10-7.60 (8H, m), 8.30-8.50 (1H, m)
16a ($C_{12}H_9N_5O_2$)	169-170	56.47 (56.69	3.55 3.50	27.44 27.70	- -)	1665, 1730, 2150 3320 [255]	2.70-3.75 (2H, m), 5.40-6.00 (2H, m), 6.45 (1H, s), 7.20-7.60 (3H, m), 7.85-8.05 (1H, m)

EXPERIMENTAL

All melting points were determined with a Yanagimoto capillary melting point apparatus (Model MP-1) and are uncorrected. Infrared (ir) spectra were recorded on a Hitachi IR-215 spectrophotometer. ^{1}H-Nuclear magnetic resonance (^{1}H-nmr) spectra were determined on a JEOL JNM MH-60 or -100 instrument in $CDCl_3$ (containing tetramethylsilane as an internal standard), unless otherwise specified. The chemical shifts are expressed in δ (ppm) values, coupling constants (*J*) are given in Hz and the following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet , br=broad. Mass spectra (ms) were measured on a Hitachi RMS-4 mass spectrometer. Physico-chemical data for the compounds obtained here are shown in Table 1.

Triethyl 1-[(2-Nitrophenyl)acetyl]-1,1,2-ethanetricarboxylate (7a): DMF (0.5 ml) and $SOCl_2$ (7.2 ml; 0.100 mol) was added to a suspended solution of 2-nitrophenylacetic acid (18.1 g, 0.100 mol) in $CHCl_3$ (90 ml), and then the mixture was stirred at 35~40°C for 2.5 h and evaporated to dryness to give 2-nitrophenylacetyl chloride, which was used to the next reaction without further purification. A solution of triethyl 1,1,2-ethanetricarboxylate (24.6 g, 0.100 mol) in EtOH (10 ml) was added dropwise to Mg-ribbon (2.5 g, 0.103 mol) in EtOH (2.5 ml)-CCl_4 (0.1 ml) at refluxing temperature. After refluxing slowed down, ether (30 ml) was added to the reaction mixture, which was stirred at 40°C for 17 h. The residue obtained after removal of the solvent was dissolved in toluene (100 ml) and added dropwise to the stirred solution of 2-nitrophenylacetyl chloride obtained above in toluene (50 ml) at -5~0°C over a period of 10 min, and the whole mixture was stirred for 10 min at the same temperature. The mixture was quenched with cold aqueous 10% AcOH, and extracted twice with toluene. The extracts were washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a brown oil, which was chromatographed on SiO_2 (*n*-hexane:AcOEt=3:1) to give **7a** (36.4 g, 89%) as a brown oil.

Triethyl 1-[(2-Nitrophenyl)acetyl]-1,1,3-propanetricarboxylate (7b): 2-Nitrophenylacetic acid (54.3 g, 0.300 mol) and triethyl 1,1,3-propanetricarboxylate (86.0 g, 0.330 mol) were allowed to react in the same manner as described for **7a** to give **7b** (95.2 g, 75%) as a pale red oil.

Intramolecular reductive cyclization — Method A-I. Triethyl 1-(1*H*-Indol-2-yl)-1,1,2-ethanetricarboxylate (8a): A solution of **7a** (21.9 g, 0.053 mol) in ether (50 ml) was added dropwise to a stirred solution of $SnCl_2$ (46.0 g, 0.024 mol) in saturated HCl-ether (550 ml) at -30°C over a period of 10 min. The reaction mixture was stirred at 25°C for 3.5 h. After removal of the solvent, the residue was dissolved in $CHCl_3$, and washed with cold brine, saturated $NaHCO_3$ and brine. The organic layer was dried

over Na_2SO_4, concentrated *in vacuo*, and the residue was crystallized from *i*-Pr_2O-*n*-hexane to give **8a** (13.4 g, 69%) as pale brown prisms.

Method A-II. Diethyl 1,2,3,4-Tetrahydro-4-oxo-9*H*-carbazol-1,1-dicarboxylate (10b): A solution of **7b** (10.6 g, 0.025 mol) in ether (90 ml) was added dropwise to a stirred solution of $SnCl_2$ (14.2 g, 0.075 mol) in saturated HCl-ether (300 ml) at -20°C over a period of 10 min. The reaction mixture was stirred at 25°C for 20 h, and worked-up in a manner similar to that described for the method A-I to give **10b** (5.0 g, 61%) as a colorless crystalline powder from AcOEt-*n*-hexane.

Method B-I. Compound (8a) and Triethyl 1-Hydroxy-1*H*-indol-2-yl-1,1,2-ethanetricarboxylate (9a): A mixture of **7a** (5.0 g, 0.012 mol), 10% Pd-C (2.0 g) in EtOH (100 ml), and 10% HCl-EtOH (1.0 ml) was hydrogenated in an atmosphere of H_2 for 4 h at 25°C, and filtered. The filtrate was concentrated *in vacuo* to give a residue, which was dissolved in $CHCl_3$ and washed with saturated $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, concentrated *in vacuo*, and the residue was chromatographed on SiO_2 ($CHCl_3$:EtOAc=19:1) to give **8a** (0.76 g,18%), and **9a** (3.30 g, 73%) as a pale yellow oil.

Method B-II. Triethyl 1-(1*H*-Indol-2-yl)-1,1,3-propanetricarboxylate (8b) and Triethyl 1-Hydroxy-1*H*-indol-2-yl-1,1,3-propanetricarboxylate (9b): A mixture of **7b** (5.0 g, 0.011 mol), 10% Pd-C (1.0 g) in EtOH (100 ml), and 10% HCl-EtOH (1.0 ml) was hydrogenated in a manner similar to that described for the method B-I to give **8b** (0.8 g, 18%) as colorless prisms from *i*-Pr_2O, and **9b** (3.1 g, 66%) as a yellow oil.

Method B-III. Compounds (8b, 9b) and Diethyl 1,2,3,4,4a,5-Hexahydro-1-oxobenzo-[*b*]indolizine-4,4-dicarboxylate (11b): A mixture of **7b** (73.2 g, 0.173 mol) and 10% Pd-C (36.5 g) in AcOH (100 ml) was hydrogenated in a manner similar to that described for the method B-I. The resulting residue was chromatographed on SiO_2 (*n*-hexane : AcOEt = 3:1) to give **8b** (55.1 g, 85%), **9b** (0.6 g, 1%) and **11b** (4.2 g, 7%) as colorless prisms from *i*-Pr_2O.

Method B-IV. Compounds (8b and 11b): A mixture of **7b** (7.3 g, 0.017 mol) and 10% Pd-C (3.6 g) in HCOOH (15 ml) was hydrogenated in a manner similar to that described for the method B-III to give **8b** (2.8 g, 44%), and **11b** (3.2 g, 56%).

Dehydroxylation of 9a: A solution of 1.35 *N* HCl in AcOH (5 ml) was added to a mixture of **9a** (500 mg, 0.0013 mol) and $SnCl_2$ (251 mg, 0.0013 mol) at 0°C. The mixture was heated at 60°C for 5 h, and worked-up in a manner similar to that described for the method A-I to give **8a** (330 mg, 70%).

Diethyl 1,2-Dihydro-1-oxo-3*H*-benzo[*b*]pyrrolizine-3,3-dicarboxylate (12a): A solution of **8a** (6.5 g, 0.018 mol) in TFA (120 ml) was refluxed for 77 h. After removal of the solvent, the residue was dissolved in AcOEt and washed with saturated $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, concentrated *in vacuo*, and the residue was crystallized from *i*-Pr_2O to give **12a** (4.8 g, 85%) as a colorless crystalline powder.

Diethyl 1,2,3,4-Tetrahydro-1-oxobenzo[*b*]indolizine-4,4-dicarboxylate (12b): A mixture of **12b** (40.0 g, 0.107 mol) and DBU (32.0 g, 0.214 mol) in toluene (700 ml) was refluxed for 3.5 h. The reaction mixture was poured into ice-water, and acidified with 10% HCl. The organic layer separated was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a pale brown oil. The resulting oil was crystallized from *i*-Pr_2O to give **12b** (28.9 g, 82%) as colorless plates.

Dehydration of 11b: A mixture of **10** (50 mg, 0.150 mmol) and 10% Pd-C (200 mg) in xylene (15 ml) was refluxed for 24 h, and filtered. The filtrate was concentrated *in vacuo* to give a residue, which was purified by SiO_2 thin layer chromatography (*n*-hexane:AcOEt = 3:1) to give **12b** (10 mg, 20%).

2,3-Dihydro-1-oxo-1*H*-benzo[*b*]pyrrolizin-3-ylcarboxylic Acid (13a) and 1,2,3,4-Tetrahydro-1-oxo-1*H*-benzo[*b*]indolizin-4-ylcarboxylic Acid (13b) — Procedure A. A solution of BBr_3 (15.0 g, 0.060 mol) in CH_2Cl_2 (50 ml) was added dropwise to a stirred solution of **12a** (4.80 g, 0.015 mol) in CH_2Cl_2 (100 ml) at -30 ~ -20°C over a period of 10 min, and then the mixture was stirred for 1 h at 25°C. After the reaction mixture was quenched with cold brine, the organic layer was concentrated *in vacuo* to give a residual oil, which was dissolved in AcOEt and extracted twice with saturated $NaHCO_3$. The aqueous layers were acidified with 10% HCl and extracted twice with AcOEt. The organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was crystallized from *i*-Pr_2O to give **13a** (2.3 g, 71%) as a colorless crystalline powder. **12b** (7.5 g, 0.022 mol) was also treated in a manner similar to that described for **13a** to give **13b** (3.8 g, 72%) as colorless prisms.

Procedure B. Compound (**12a**) (1.9 g, 0.006 mol) was added to a stirred solution of $AlCl_3$ (3.2 g, 0.024 mol) in tetrahydrothiophene (8.5 g, 0.120 mol) at 25°C. The mixture was heated at 80~90°C for 1.5 h, stirred at 25°C for 24 h, poured into ice-H_2O (100 ml), and taken up into AcOEt. The AcOEt layer was extracted three times with saturated $NaHCO_3$, and the aqueous layers were acidified with 10% HCl, and then extracted twice with AcOEt. The organic extracts were treated in a manner similar to that described for the procedure A to give **13a** (1.1 g, 88%). On the other hand, **13b** was obtained by the following manner: $AlCl_3$ (35.0 g, 0.269 mol) was added to a stirred solution of **12b** (14.3 g, 0.044 mol) in $ClCH_2CH_2Cl$ (300

ml) and tetrahydrothiophene (23.7 g, 0.269 mol) under 25°C. The whole was refluxed for 3 h, and worked-up in a manner similar to that described for **13a** to give **13b** (9.1 g, 91%) .

Ethyl 2,3-Dihydro-1-oxo-1*H*-benzo[*b*]pyrrolizin-3-ylcarboxylate (14a): A solution of **13a** (8.0 g, 0.037 mol) in 10% HCl-EtOH (150 ml) was stirred at 25°C for 4 h, and concentrated *in vacuo*. The residue was dissolved in AcOEt (200 ml), which was washed with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was crystallized from EtOH to give **14a** (8.3 g, 92%) as colorless crystals.

2,3-Dihydro-1-oxo-1*H*-benzo[b]pyrrolizin-3-ylbenzylcarbamate (15a) and 2,3-Dihydro-1-oxo-1*H*-benzo[*b*]pyrrolizin-3-ylcarbamoyl Azide (16a): A mixture of **13a** (430 mg, 0.002 mol), DPPA (606 mg, 0.002 mol) and Et_3N (226 mg, 0.002 mol) in benzene (30 ml) was refluxed for 1 h. A solution of benzyl alcohol (238 mg, 0.002 mol) in benzene (5 ml) was then added to the reaction mixture, and the whole was refluxed for 22 h, and filtrated to remove insoluble materials. The filtrate was washed with 5% citric acid, saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a yellow oil. The resulting oil was chromatographed on SiO_2 ($CHCl_3$:AcOEt = 9:1) to give 150 mg (23%) of **15a** as a pale yellow crystalline powder, and **16a** (89 mg, 18%) as a colorless crystalline powder.

1,2,3,4-Tetrahydro-1-oxo-1*H*-benzo[*b*]indolizin-4-ylbenzylcarbamate (15b): $SOCl_2$ (8.8 g, 0.074 mol) in CH_2Cl_2 (20 ml) was added to a solution of **13b** (8.5 g, 0.037 mol) in CH_2Cl_2 (130 ml) at 25° over a period of 30 min, and the mixture was stirred at 50°C for 1.5 h, and concentrated *in vacuo* to give a dark brown residue. A solution of NaN_3 (3.6 g, 0.055 mol) in H_2O (15 ml) was added at 5°C over a period of 30 min to the solution of the resulting residue in acetone (75 ml), and the mixture was stirred at 25°C for 1.5 h. The whole was poured into ice-H_2O, extracted twice with ether. The extracts were washed with brine, dried over Na_2SO_4, and then concentrated *in vacuo* to give a brown oil. A solution of benzyl alcohol (12.0 g, 0.110 mol) in toluene (150 ml) was added to the oil, and the whole was refluxed at 130°C for 1.5 h, and concentrated *in vacuo*. The resulting residue was crystallized from AcOEt-*i*-Pr_2O to give **15b** (10.6 g, 86%) as colorless prisms.

3-Amino-2,3-dihydro-1*H*-benzo[*b*]pyrrolizin-1-one Hydrochloride (4a • HCl): A mixture of **15a** (640 mg, 0.002 mol) and 10% Pd-C (50 mg) in EtOH (50 ml) was hydrogenated in an atmosphere of H_2 at 25°C for 1.5 h, and filtered. The filtrate was concentrated *in vacuo* to give a pale yellow oil, which was treated with 10% HCl-MeOH, and concentrated to give a solid. Recrystallization from ether-*n*-hexane gave **4a** • HCl (400 mg, 90%) as a colorless crystalline powder.

4-Amino-3,4-dihydrobenzo[*b*]indolizin-1(2*H*)-one (4b-1): A mixture of **15b** (5.5 g, 0.017 mol) and 10% Pd-C (5.5 g) in AcOEt (550 ml) was hydrogenated in an atmosphere of H_2 at 25°C for 3 h, and filtered. The filtrate was concentrated *in vacuo* to give a pale green oil, which was crystallized from AcOEt-*i*-Pr_2O (1:3) to give **4b-1** (3.2 g, 96%) as pale green prisms.

4-Benzylideneamino-3,4-dihydrobenzo[*b*]indolizin-1(2*H*)-one (4b-2): Benzaldehyde (1.9 g, 0.018 mol) was added to a solution of **4b-1** (2.4 g, 0.012 mol) in MeOH (20 ml) and the solution was stirred at 25°C for 2 h to give the precipitate which was collected by suction. Recrystallization from MeOH gave **4b-2** (2.9 g, 83%) as colorless needles.

4-Benzylamino-3,4-dihydrobenzo[*b*]indolizin-1(2*H*)-one (4b-3): $NaBH_4$ (236 mg, 0.006 mol) was added portionwise to a solution of **4b-2** (3.7 g, 0.013 mol) in 50% THF-MeOH (300 ml) at -5 ~ 0°C over a period of 2 h. The reaction mixture was stirred for 1 h at the same temperature, poured into ice-H_2O, and extracted twice with AcOEt . The extracts were washed with brine, and concentrated *in vacuo* to give a yellow oil, which was crystallized from *i*-Pr_2O to give **4b-3** (2.8 g, 75%) as colorless prisms.

4-*n*-Butylamino-3,4-dihydrobenzo[*b*]indolizin-1(2*H*)-one Hydrochloride (4b-4 • HCl): *n*-Butyraldehyde (1.3 g, 0.018 mol) was added to a solution of **4b-1** (1.8 g, 0.009 mol) in MeOH (20 ml) and the mixture was stirred at 25°C for 2 h. $NaBH_4$ (0.2 g, 0.005 mol) was added portionwise to the reaction mixture, which was worked-up in a manner similar to that described for **4b-3** to give a pale green oil. The resulting oil was treated with 10% HCl-MeOH to give a solid, which was crystallized from EtOH to give **4b-4** • HCl (1.3 g, 69%) as colorless prisms.

4-Benzylmethylamino-3,4-dihydrobenzo[*b*]indolizin-1(2*H*)-one (4b-5): A mixture of **4b-3** (1.8 g, 0.006 mol), 37% HCHO (10 ml) and HCOOH (10 ml) was heated at 80~90°C for 1 h, and concentrated *in vacuo*. The residue was dissolved in AcOEt, washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a solid. Recrystallization from *i*-Pr_2O gave **4b-5** (1.9 g, 98%) as colorless prisms.

4-Dimethylamino-3,4-dihydrobenzo[*b*]indolizin-1(2*H*)-one Hydrochloride (4b-6 • HCl): A mixture of **4b-1** (0.8 g, 0.004 mol), 37% HCHO (4 ml) and HCOOH (4 ml) was treated in a manner similar to that described for **4b-5** to give a yellow oil. The resulting oil was treated with 10% HCl-MeOH to give a solid, which was crystallized from EtOH to give **4b-6** • HCl (0.7 g, 71%) of as colorless prisms.

4-Methylamino-3,4-dihydrobenzo[*b*]indolizin-1(2*H*)-one Hydrochloride (4b-7 • HCl): A mixture of **4b-5** (1.9 g, 0.006 mol) and 10% Pd-C (2.0 g) in 70% aqueous AcOH (100 ml) was

hydrogenated in an atmosphere of H_2 at 25°C for 2.5 h, and filtered. The filtrate was concentrated *in vacuo* to give a yellow oil, which was dissolved in AcOEt, washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting oil was treated with 10% HCl-MeOH to give a solid, which was crystallized from EtOH to give **4b-7** • HCl (1.0 g, 72%) as colorless prisms.

REFERENCES

1. (a) M. Lounasmaa and A. Tolvanen, *The Alkaloids*, ed. by G. A. Cordell, **42**, p. 1, Academic Press, Inc., San Diego, California, 1992. (b) A. Szabo and Z. Nagy, *Arzneimittel Forsch.*, 1960, **10**, 811. (c) P. Lacroix, M. J. Quiniou, Ph. Linee, and J. B. Lepolles, *Arzneimittel Forsch.*, 1979, **29**, 1094. (d) Y. Sato, T. Mizoguchi, Y. Kudo, and R. Ishida, *Japan Patent*, 54-148636, and 55-73680 (*Chem. Abstr.*, 1980, **93**, 220719b, *ibid.*, 1982, **96**, 217867e).
2. Y, Simoji, F. Saito, K. Tomita, and Y. Morisawa, *Heterocycles*, 1991, **32**, 2389.
3. (a) F. L. Benton and T. E. Dillon, *J. Am. Chem. Soc.*, 1942, **64**, 1128. (b) M. Node, K. Nishide, M. Sai, K. Fuji, and E. Fujita, *J. Org. Chem.*, 1981, **46**, 1991.
4. X-Ray crystallography of **14a** : Molecular formula, $C_{14}H_{13}NO_3$; molecular weight, 243.26; space group, P 21/c (z=4), a=12.376 (2), b=8.472 (2), c=12.929 (2) Å, α=90.00 (0)°, β=114.57 (1)°, γ=90.00 (0)°, V=1232.9 (3) $Å^3$, Dx=1.310 g/cm^3. Final R factor=0.064.
5. K. Ninomiya, T. Shioiri, and S. Yamada, *Tetrahedron*, 1974, **30**, 2151.
6. M. L. Moore, *Org. Reactions*, Vol. **5**, p. 323, ed. by R. Adams, R. E. Krieger Publishing, Co., New York, 1968.

Received, 3rd February, 1995