Chemistry of Tetrahydro-1,3-oxazin-2-one: New Method for the Synthesis of Indoloquinolizidine Derivatives

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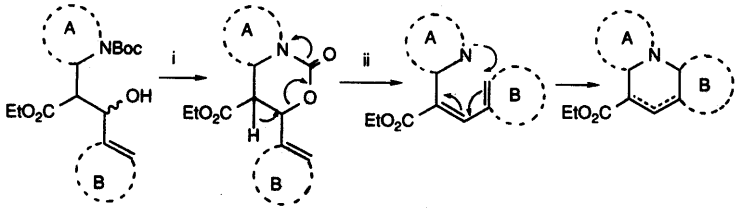
The aldol condensation of the *N*-Boc-tetrahydro-β-carboline-1-acetate (4) with acrolein in the presence of lithium diisopropylamide (LDA) gave an allyl alcohol (6), which was then treated with methanesulfonyl chloride and triethylamine to give a mixture of the mesylate (8) (55%) and the indolopyrido-3,5-oxazin-4-one (10) (14%). When 8 was treated with 1,8-diazabicyclo[5.4.0.]-7-undecene (DBU) in dimethylsulfoxide (DMSO) at room temperature, the azetopyridoindoles (12 and 13) were obtained unexpectedly. Alternative preparation of the indolopyrido-3,5-oxazin-4-ones (15 and 16), which are stereoisomers of 10, from 6 followed by heating with DBU in DMSO gave several indoloquinolizidines (18, 19 and 20), which are key intermediates for the synthesis of the indole alkaloids vindolosine and vindoline.

Keywords tetrahydro-1,3-oxazin-2-one; tetrahydro-β-carboline; azetidine; indolopyrido-3,5-oxazin-4-one; azetopyridoindole; indoloquinolizidine; 1,8-diazabicyclo[5.4.0.]-7-undecene; X-ray analysis

Cyclic carbamates such as oxazolidin-2-ones or tetrahydro-1,3-oxazin-2-ones, which are generally prepared from allylic[1] or homoallylic[2] acyclic carbamates by halolactonization, are versatile intermediates in organic synthesis, since hydrolytic cleavage of the heterocyclic rings readily provides the 1,2- or 1,3-amino alcohol moieties found in a number of biologically important compounds. Another cyclocarbamation, involving treatment of *N*-benzyloxycarbonyl 1,2-amino alcohols with thionyl chloride, has also been reported to give oxazolidin-2-one.[3]

Recently, we have reported[4] a novel cyclocarbamation of *N-tert*-butoxycarbonyl (Boc)-1,3-amino alcohol (I) by treatment with methanesulfonyl chloride (MsCl) and triethylamine (TEA) to give tetrahydro-1,3-oxazin-2-one (II) *via* *SN*1 type C–O bond formation of the N–COO^- group, and also its efficient transformation to the tetrahydropyridine skeleton (IV) by treatment with 1,8-diazabicyclo[5.4.-0]-7-undecene (DBU) in dimethylsulfoxide (DMSO) *via* the diene intermediate (III).[5] This methodology was applied to the synthesis of some natural products.[6] We report here new syntheses of indoloquinolizidine derivatives by application of our methodology to compounds having a tetrahydro-β-carboline moiety in the A-part of I.

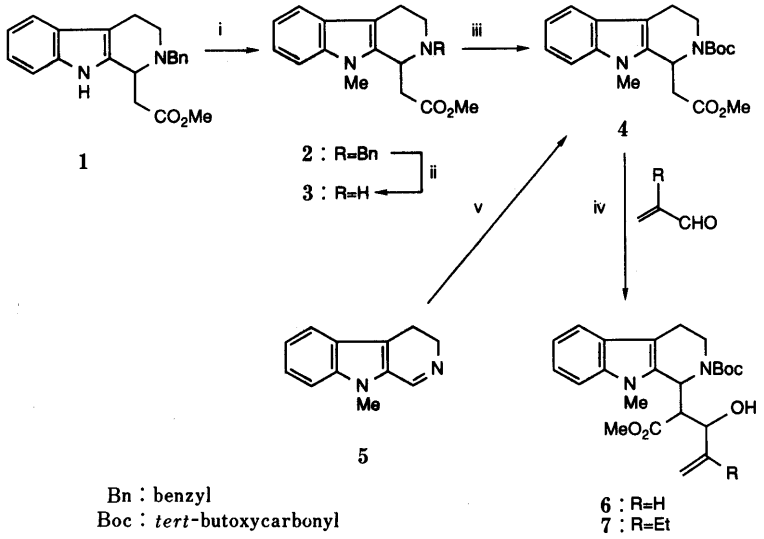
Treatment of the tetrahydro-β-carbolineacetate (**1**),[7] which was prepared by Pictet–Spengler condensation of *N*-benzyltryptamine with dimethyl acetylenedicarboxylate, with methyl iodide and sodium hydride (NaH) followed by catalytic debenzylation of the resulting **2** afforded **3** in 81% overall yield. Reaction of **3** with di-*tert*-butyl dicarbonate (Boc_2O) in tetrahydrofuran (THF) gave the carbamate (**4**) in 97% yield (method A). Compound **4** was alternatively obtained by the following one-pot operation based on the method of Nakagawa *et al.*[8] *N*-Methyl-3,4-dihydro-β-carboline (**5**)[9] was alkylated with lithio methyl acetate in the presence of boron trifluoride etherate ($BF_3 \cdot OEt_2$) followed by quenching with an excess of Boc_2O to give **4** in 90% overall yield (method B). However, method A was preferable to obtained **4** in a large quantity. Aldol condensation of **4** with acrolein or 2-ethylacrolein in the presence of lithium diisopropylamide (LDA) in THF at −78 °C gave the allyl alcohol (**6** or **7**) as an oily mixture of diastereomers, in good yield, after purification by column chromatography on SiO_2. The product (**6**) was treated with MsCl and TEA in dichloromethane (CH_2Cl_2) at room temperature to give a mixture of the mesylate (**8**) (less polar) and the indolopyrido-3,5-oxazin-4-one (**10**) (more polar), which were, without isolation, submitted to the usual cleavage of the Boc group by 2.3 N HCl–EtOAc. Cyclization of the resulting hydrochloride was attempted by treatment with DBU (2 eq) in DMSO at room temperature according to our previous method[5] in expectation of the formation of the indoloquinolizidine. The crude oil finally obtained was purified by column chromatography to give **12** [mass spectrum (MS) *m/z*: 296 (M^+)] (50%), **10** [MS *m/z*: 340 (M^+)] (9.5%), and **13** [MS *m/z*: 296 (M^+)] (6.5%). The proton nuclear magnetic resonance (^{1}H-NMR) spectra of **12** (and **13**) showed the presence of terminal methylene protons at δ 5.22 (5.08), 5.39 (5.21), and 5.91 (5.93) as well as the protons of the tetrahydro-β-carboline skeleton. Selected ^{1}H-NMR and carbon-13 nuclear magnetic



I II III IV

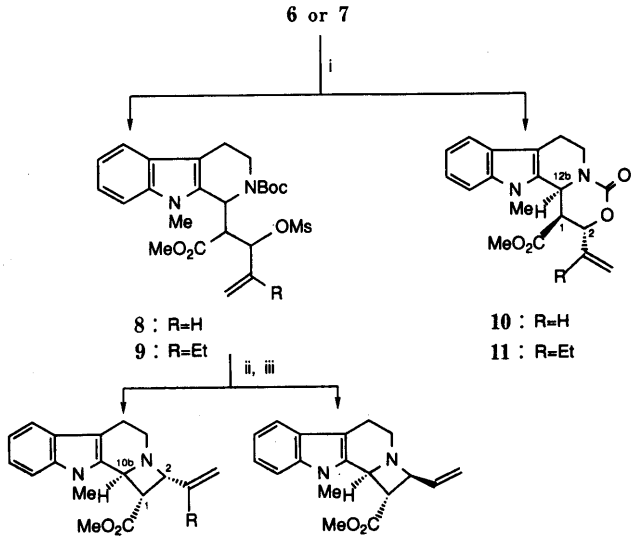
reagents: i, MsCl/TEA; ii, DBU/DMSO B=aryl or ethenyl and cycloalkenyl

Chart 1



reagents : i, NaH/MeI; ii, 10% Pd-C/H_2; iii, (*tert*-BuOCO)$_2$O; iv, LDA; v, $MeCO_2Me$/LDA/BF_3·OEt_2 then (*tert*-BuOCO)$_2$O

Chart 2

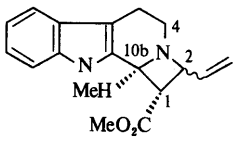


reagents: i, $MsCl/Et_3N$; ii, 2.3 N HCl/EtOAc; iii, DBU/DMSO/r.t.

Chart 3

resonance (^{13}C-NMR) data for both compounds are summarized in Table I. The ^{13}C-NMR spectra indicated the presence of three tertiary carbon atoms in each case. On the basis of these results, the structures of **12** and **13** were deduced to be methyl 2-ethenyl-9-methyl-1,4,5,10b-tetrahydro-2*H*-azeto[1′,2′ : 1,2]pyrido[3,4-*b*]indole-1-carboxylates, which are interesting substrates for Meisenheimer rearrangement of the corresponding *N*-oxides.[10] The stereochemistries of **12** (1,2-*cis*) and **13** (1,2-*trans*) were determined from the ^{1}H-NMR spectral data, based on the general rule developed for azeto[2,1-*a*]isoquinolines,[11] in which the vicinal coupling constants of the azetidines $^3J_{(H,H)}$*cis* (7—8 Hz) are larger than $^3J_{(H,H)}$*trans* (2—3 Hz). The structure of the third component (**10**) was readily

TABLE I. Selected ^{13}C- and ^{1}H-NMR Data for Compounds **12** and **13** (δ $CDCl_3$)



Number	Carbon		Proton (*J*, Hz)	
	12	**13**	**12**	**13**
1	48.6 (d)	47.7 (d)	3.13 (dd, *J*=8, 3)	2.88 (t, *J*=4)
2	68.5 (d)	61.2 (d)	4.30 (t, *J*=8)	4.54 (dd, *J*=10, 4)
4	41.4 (t)	41.1 (t)		
10b	54.1 (d)	56.5 (d)	5.10 (br s)	5.02 (br s)

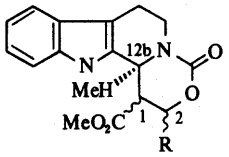
determined as 2-ethenyl-1-methoxycarbonyl-12-methyl-1,6,7,12b-tetrahydro-2*H*,4*H*-indolo[2,3-*c*][1,3]oxazin-4-one on the basis of the spectral data (see Experimental). Stereochemical assignment of **10** will be discussed later. After usual mesylation of **6**, the crude product was purified by column chromatography to give the mesylate (**8**) as an oily mixture of diastereomers in 55% yield, together with **10** in 14% yield. De-*tert*-butoxycarbonylation of **8** followed by DBU treatment gave a mixture of **12** (54%) and **13** (6.5%). Similarly, usual mesylation of **7** followed by column-chromatographic purification gave a mixture of the mesylate (**9**, 33%) and the indolopyrido-3,5-oxazin-4-one (**11**, 11%). De-*tert*-butoxycarbonylation of **9** followed by DBU treatment gave the azetidine **14** in 43% yield; its ^{1}H-NMR spectrum was very similar to that of **12**. Although the mechanistic details have not been established, it is suggested that the indole moiety may participate in the formation of azetidines.

Another approach to the indoloquinolizidine derivatives was investigated. De-*tert*-butoxycarbonylation of **6** followed by condensation of the resulting amino alcohol with carbonyl diimidazole (Im_2CO) in refluxing benzene afforded

oxazinones (**15** and **16**) in 54 and 23% yields, respectively. Their infrared (IR) and ^{1}H-NMR spectra were similar to those of **10**. Table II shows selected ^{1}H-NMR spectral data for **10**, **11**, **15**, and **16**. The coupling constants of the neighboring three methine protons, however, did not give the necessary information for determining the stereochemistry. But, the stereochemistry of **16** alone could be established to be as depicted in Chart 4 on the basis of the nuclear Overhauser effect (NOE) between H-1, H-2, and H-12b of the corresponding dihydro derivative (**17**), which was obtained by catalytic hydrogenation of **16** with 5% palladium on carbon (Pd–C). Irradiation of H-2 at δ 4.40 caused distinct enhancements of the signals at δ 3.55 and 5.15 due to H-1 and H-12b, respectively. However, stereochemistry of the other compounds (**10** and **15**) could not be resolved clearly by the same method. Thus, X-ray crystallographic analyses of compounds **10** and **15** were carried out and the molecular structures determined are shown in Fig. 1.

The mixture of tetrahydro-1,3-oxazin-2-ones (**15** and **16**)[12] thus obtained was heated with DBU (1.1 eq) in DMSO at 120 °C for 4 h, giving a mixture of three products (total yield 47.4%), **18**, **19**, and **20**, *via* successive decarboxylation–recyclization sequences. These compounds are key intermediates for the synthesis of indole alkaloids vindolosine and vindoline.[13] The spectroscopic data (IR, MS and ^{1}H-NMR) were in good agreement with reported values.[13]

TABLE II. Selected ^{1}H-NMR Data for Compounds **10**, **11**, **15**, **16**, and **17** [δ $CDCl_3$, J(Hz)]

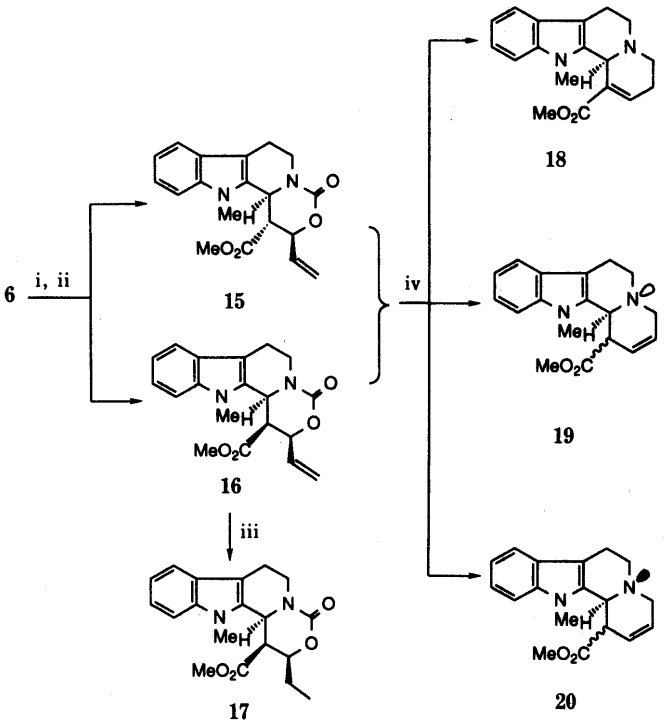


R = CH=CH$_2$, C(Et)=CH$_2$, Et

Compd.	H-1	H-2	H-12b
10	3.41 (dd, J=4.4, 1.8)	5.18 (dd, J=4.0, 1.0)	5.11 (br d, J=4.4)
11	3.47 (dd, J=4.5, 2.5)	5.05 (br s)	5.05 (br s)
15	3.10 (t, J=5.6)	4.96 (t, J=5.6)	5.39 (d, J=5.6)
16	3.62 (dd, J=5.8, 2.8)	5.04 (br s)	5.23 (d, J=5.8)
17	3.55 (1H, dd, J=5.3, 3.0)	4.40 (m)	5.15 (d, J=6.0)

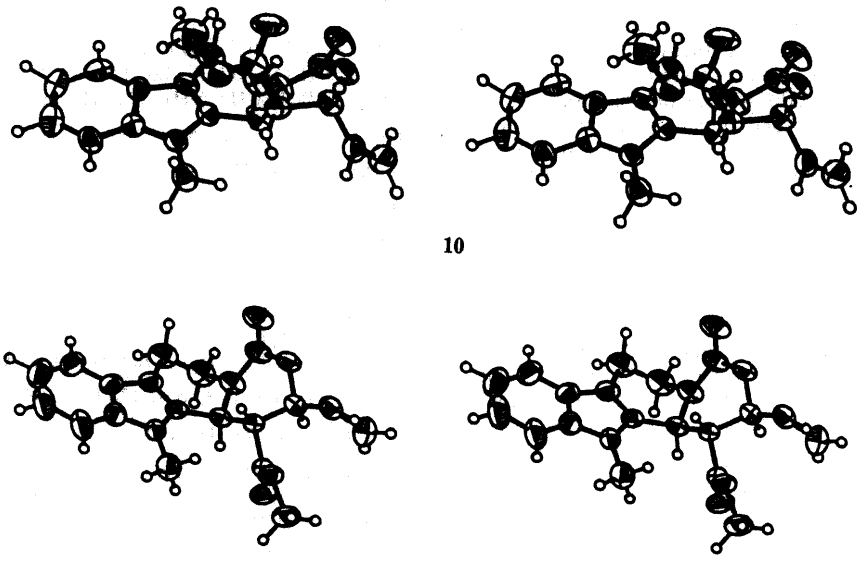
Experimental

All melting points were measured on a Yanagimoto apparatus and are uncorrected. IR absorption spectra were recorded on a Shimadzu IR-435 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were obtained with a Varian Gemini-200 spectrometer; signals are given in ppm. Low-resolution (MS) and high-resolution mass spectra (HRMS) were obtained on a Hitachi M-80 instrument. All reactions were carried out under a nitrogen



reagents : i, 2.3 N HCl/EtOAc; ii, Im_2CO; iii, 5% Pd-C/H_2; iv, DBU/DMSO/120 °C

Chart 4



10 15

Fig. 1. Stereoscopic View of the Molecules **10** and **15**

atmosphere. For column chromatography, SiO_2 (Merck 9385) was used.

2-Benzyl-1-carbomethoxymethyl-9-methyl-1,2,3,4-tetrahydro-β-carboline (2) A solution of **1** (9.72 g, 29.1 mM) in dimethylformamide (DMF) (25 ml) was added dropwise to a suspension of 60% NaH (1.51 g, 37.8 mM) in DMF (15 ml) with stirring at room temperature. The mixture was stirred for 1 h, then a solution of methyl iodide (3.62 ml, 58.2 mM) in DMF (13 ml) was added dropwise with external cooling with water, and the whole was stirred for 2 h. The reaction mixture was poured into ice-water (500 ml), and extracted with EtOAc (100 ml × 3). The extract was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was agitated with a mixture of hexane–EtOH (3 : 1), and the resulting precipitate was collected by filtration to give **2** (8.39 g, 83%), which was recrystallized from EtOH to give pale yellow crystals, mp 103—105 °C. IR ν_{max} (Nujol) cm^{-1}: 1735 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.5—3.3 (6H, m, $CH_2 \times 3$), 3.62, 3.70 (each 3H, each s, NCH_3 and/or $COOCH_3$), 3.69, 3.74 (each 1H, each d, J=13 Hz, NCH_2Ar), 4.33 (1H, dd, J=10.5, 3.5 Hz, 1-H), 7.1—7.4 (3H, m, ArH), 7.57 (1H, d, J=7.5 Hz, 8-H). MS *m/z* 348 (M^+). *Anal.* Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.87; H, 6.99; N, 8.00.

1-Carbomethoxymethyl-9-methyl-1,2,3,4-tetrahydro-β-carboline (3) A solution of **2** (18.0 g, 51.7 mM) in MeOH (400 ml) containing concentrated HCl (18 ml) was hydrogenated using a Skita apparatus (initial pressure: 5.0 kg/cm^2) with 10% Pd–C (5.8 g) for 10 h. The catalyst was removed by filtration through a celite pad, and the filtrate was concentrated *in vacuo*. The residue was neutralized with saturated $NaHCO_3$ solution, and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residual oil (12.9 g, 97%) was found to be almost pure **3**. IR ν_{max} ($CHCl_3$) cm^{-1}: 3330 (NH), 1720 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.60—2.80 (4H, m, $CH_2 \times 2$), 3.15 (2H, m, CH_2COO), 3.62, 3.75 (each 3H, each s, NCH_3 and/or $COOCH_3$), 4.59 (1H, dd, J=10.0, 2.5 Hz, 1-H), 7.05—7.29 (3H, m, ArH), 7.50 (1H, d, J=7.7 Hz, 8-H). MS *m/z*: 258 (M^+). HRMS Calcd for $C_{15}H_{18}N_2O_2$: 258.1367. Found: 285.1368.

2-*tert*-Butoxycarbonyl-1-carbomethoxymethyl-9-methyl-1,2,3,4-tetrahydro-β-carboline (4). Method A: A solution of Boc_2O (11.3 g, 50.2 mM) in THF (10 ml) was added dropwise to a solution of **3** (12.9 g, 50.2 mM) in THF (60 ml) under ice cooling and the whole was stirred at room temperature for 1.5 h. Removal of the solvent gave a solid, which was recrystallized from EtOH to give **4** (17.6 g, 97%) as colorless crystals, mp 116—118 °C. IR ν_{max} (Nujol) cm^{-1}: 1740, 1680 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.49 [9H, s, $C(CH_3)_3$], 2.78—2.95 (4H, m, $CH_2 \times 2$), 3.70, 3.72 (each 3H, each s, NCH_3 and/or $COOCH_3$), 4.32—4.52 (2H, m, CH_2COO), 5.79 (1H, m, 1-H), 7.10—7.40 (3H, m, ArH), 7.48 (1H, d, J=7.5 Hz, 8-H). MS *m/z*: 358 (M^+). *Anal.* Calcd for $C_{20}H_{26}N_2O_4$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.91; H, 7.30; N, 7.75.

Method B: $BF_3 \cdot OEt_2$ (0.14 ml, 1.1 mM) was added to a solution of **5** (202 mg, 1 mM) in THF (7 ml) at room temperature, and the mixture was cooled to −23 °C. Methyl acetate (0.28 ml, 3.5 mM) was added to a solution of LDA, prepared from diisopropylamine (0.56 ml, 4 mM) and *n*-butyl lithium (*n*-BuLi) (15% hexane solution, 2.52 ml, 4 mM), in THF (7 ml) at −78 °C to prepare lithio methyl acetate. This solution was added to the mixture and the whole was stirred at −23 °C for 30 min. The reaction was quenched by the addition of a solution of Boc_2O (1.09 g, 5 mM) in THF (7 ml) at −23 °C. After the mixture had been stirred for 2 h, the solvent was removed by evaporation. The residue was agitated with a mixture of EtOH–hexane (1 : 1) and the resulting solid was collected by filtration, washed with cold EtOH, and dried to give **4** (213 mg, 60%). The filtrate was concentrated, and the residue was purified by column chromatography (20% EtOAc in hexane) to give **4** (109 mg, 30%) (total yield 90%). This was identical with the sample of **4** obtained by method A, based on comparison of their IR and ^{1}H-NMR spectra.

Methyl 2-(2-*tert*-Butoxycarbonyl-9-methyl-1,2,3,4-tetrahydro-β-carbolin-1-yl)-3-hydroxy-4-pentenoate (6) A solution of **4** (7.16 g, 20 mM) in THF (50 ml) was added dropwise to a solution of LDA [prepared from diisopropylamine (3.4 ml, 24 mM) and *n*-BuLi (15% hexane solution, 15.4 ml, 24 mM)] in THF (50 ml) at −78 °C, and the mixture was stirred at this temperature for 20 min. Then, 90% acrolein (pre-dried for 30 min with molecular sieves 4A) (2.7 ml, 40 mM) was added at once to this solution, and the whole was stirred at −78 °C for 20 min. The reaction mixture was quenched with water, and THF was removed by evaporation. The residue was extracted with EtOAc–benzene (1 : 1), and the extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residual oil was purified by column chromatography (15% EtOAc in hexane) to give pure **6** (8.11 g, 98%) as an oil. IR ν_{max} (neat) cm^{-1}: 3430 (OH), 1725, 1680 (CO). The ^{1}H-NMR spectrum was not sufficiently well resolved to permit assignment of the signals all. Selected signals were as follows: ^{1}H-NMR ($CDCl_3$) δ: 1.45 [9H, s, $C(CH_3)_3$], 2.7—3.2 (4H, m, $CH_2 \times 2$), 3.30 (3H, s, NCH_3), 3.62 (3H, s, $COOCH_3$), 7.18—7.35 (3H, m, ArH), 7.47 (1H, d, J=7.5 Hz, ArH). MS *m/z*: 414 (M^+). HRMS Calcd for $C_{23}H_{30}N_2O_5$: 414.2153. Found: 414.2161.

Methyl 2-(2-*tert*-Butoxycarbonyl-9-methyl-1,2,3,4-tetrahydro-β-carbolin-1-yl)-3-hydroxy-4-methylenehexanoate (7) By a similar procedure to that described for the preparation of **6**, the crude product which was obtained from **4** (1.08 g, 3 mM), LDA (3.3 mM), and 2-ethylacrolein (0.44 ml, 6 mM) was purified by column chromatography (15% EtOAc in hexane) to give pure **7** (928 mg, 70%) as an oil. IR ν_{max} (neat) cm^{-1}: 3450 (OH), 1730, 1685 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, t, J=8.0 Hz, $CH_2\underline{CH}_3$), 1.45 [9H, s, $C(CH_3)_3$], 1.97—2.20 (2H, m, $C\underline{H}_2CH_3$), 2.75—2.90 (2H, m, 4-CH_2), 3.19 (3H, s, NCH_3), 3.44—3.59 (2H, m, 3′-H_2), 3.68 (3H, s, $COOCH_3$), 4.20 (1H, d, J=6.0 Hz, $C\underline{H}OH$), 4.67 (1H, td, J=7.5, 6.0, CHCOO), 4.89, 5.09 (each 1H, each s, $=CH_2$), 5.76 (1H, d, J=6.0 Hz, 1-H), 7.0-7.29 (3H, m, ArH), 7.44 (1H, d, J=7.5 Hz, 8-H). MS *m/z*: 442 (M^+). HRMS Calcd for $C_{25}H_{34}N_2O_5$: 442.2466. Found: 442.2458.

2-Ethenyl-1-methoxycarbonyl-12-methyl-1,6,7,12b-tetrahydro-2*H*,4*H*-indolo[2,3-*c*]pyrido[1,2-*c*][1,3]oxazin-4-one (10), *cis*-Methyl 2-Ethenyl-10-methyl-1,4,5,10b-tetrahydro-2*H*-azeto[1′,2′ : 1,2]pyrido[3,4-*b*]indole-1-carboxylate (12), and *trans*-Methyl 2-Ethenyl-10-methyl-1,4,5,10b-tetrahydro-2*H*-azeto[1′,2′ : 1,2]-pyrido[3,4-*b*]indole-1-carboxylate (13) A solution of MsCl (1.6 ml, 20.6 mM) in CH_2Cl_2 (3 ml) was added dropwise to a solution of **6** (5.69 g, 13.7 mM) and triethylamine (5.8 ml, 41 mM) in CH_2Cl_2 (40 ml) at 0 °C, and the mixture was stirred at room temperature for 1 h, The reaction mixture was quenched with water, and extracted with $CHCl_3$. The extract was washed with water, and brine, dried over Na_2SO_4, and concentrated. The residue, which is a mixture of mesylate and oxazinone, was, without purification, dissolved in 2.3 N HCl in EtOAc (65 ml) and the mixture was stirred at room temperature for 2.5 h. After removal of the solvent by evaporation *in vacuo*, the residue was dissolved in DMSO (20 ml) containing DBU (4.1 ml, 27.4 mM). The mixture was allowed to stand for 2.5 h, diluted with water (200 ml), then extracted with EtOAc. The extract was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was subjected on column chromatography (40% EtOAc in hexane) to give **12** (2.04 g, 50% overall yield from **6**) from the first eluate. Recrystallization from EtOH gave colorless crystals, mp 97—99 °C. IR ν_{max} (Nujol) cm^{-1}: 1720 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.7—3.1 (4H, m, $CH_2 \times 2$), 3.13 (1H, dd, J=8.0, 3.0 Hz, 1-H), 3.55 (3H, s, NCH_3), 3.80 (3H, s, $COOCH_3$), 4.30 (1H, t, J=8.0 Hz, 2-H), 5.10 (1H, br s, 10b-H), 5.22 (1H, d, J=10.0 Hz, $H\!\!>\!\!\underline{H}$), 5.39 (1H, d, J=17.0 Hz, $H\!\!>\!\!\underline{H}$), 5.91 (1H, ddd, J=17.0, 10.0, 8.0 Hz, =CH), 7.20 (3H, m, ArH), 7.55 (1H, d, J=7.5 Hz, 8-H). ^{13}C-NMR ($CDCl_3$) δ: 16.5 (t), 29.8 (q), 41.1 (t), 48.6 (d), 52.5 (q), 54.1 (d), 61.2 (d), 108.1 (s), 109.3 (d), 118.8 (d), 119.0 (d), 121.0 (d), 127.3 (s), 134.0 (s), 136.4 (s), 137.3 (d), 172.0 (s). MS *m/z*: 296 (M^+). *Anal.* Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.93; H, 6.82; N, 9.42. The second eluate with the same solvent gave **10** (0.44 g, 9.5% overall yield from **6**). Recrystallization from EtOH gave colorless crystals, mp 170—172 °C. IR ν_{max} (Nujol) cm^{-1}: 1720, 1680 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.7—3.1 (3H, m, 7-CH_2, 6-H), 3.33 (3H, s, NCH_3), 3.41 (1H, dd, J=4.0, 2.0 Hz, 1-H), 4.68 (3H, s, $COOCH_3$), 4.76 (1H, br d, J=12.0 Hz, 6-H), 5.11 (1H, br d, J=4.0 Hz, 12b-H), 5.18 (1H, br q, J=2.0 Hz, 2-H), 5.49 (1H, d, J=10.0 Hz, $H\!\!>\!\!\underline{H}$), 5.55 (1H, d, J=16.0 Hz, $H\!\!>\!\!\underline{H}$), 5.98 (1H, ddd, J=16.0, 10.0, 4.0 Hz, =CH), 7.19 (3H, m, ArH), 7.50 (1H, d, J=7.5 Hz, 8-H). MS *m/z* 340 (M^+). *Anal.* Calcd for $C_{19}H_{20}N_2O_4$: C, 67.04; H, 5.92; N, 8.23. Found: C, 67.08; H, 5.91; N, 8.01. The third eluate with the same solvent gave **13** (263 mg, 6.5% overall yield from **6**). Recrystallization from EtOH–hexane (3 : 1) gave colorless crystals, 117—119 °C. IR ν_{max} (Nujol) cm^{-1}: 1720 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.70—3.10 (4H, m, $CH_2 \times 2$), 2.88 (1H, t, J=4.0 Hz, 2-H), 3.59 (3H, s, NCH_3), 3.78 (3H, s, $COOCH_3$), 4.54 (1H, dd, J=10.0, 4.0 Hz, 2-H), 5.02 (1H, br s, 12b-H), 5.08 (1H, d, J=10.0 Hz, $H\!\!>\!\!\underline{H}$), 5.21 (1H, d, J=17.0 Hz, $H\!\!>\!\!\underline{H}$), 5.93 (1H, dt, J=17.0, 10.0 Hz, =CH), 7.15 (3H, m, ArH), and 7.49 (1H, d, J=7.5 Hz, 8-H). ^{13}C-NMR ($CDCl_3$) δ: 21.8 (t), 30.0 (q), 41.1 (t), 47.7 (d), 52.7 (q), 56.5 (d), 68.5 (d), 108.0 (s), 109.3 (d), 119.0 (d), 119.6 (d), 120.6 (t), 122.3 (d), 127.6 (s), 135.1 (s), 137.7 (s), 138.2 (d), 173.7 (s). MS *m/z*: 296 (M^+). *Anal.* Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.82; H, 6.84; N, 9.36.

Reaction of 6 with MsCl and TEA A solution of MsCl (0.1 ml, 1.29 mM)

in CH_2Cl_2 (3 ml) was added dropwise to a solution of **6** (385 mg, 0.86 mM) and TEA (0.36 ml, 2.58 mM) in CH_2Cl_2 (2 ml) at 0 °C, and the mixture was stirred at room temperature for 1 h. Work-up gave a crude oil, which was submitted to column chromatography (20% EtOAc in hexane) to give methyl 2-(2-*tert*-butoxycarbonyl-9-methyl-1,2,3,4-tetrahydro-β-carbolin-1-yl)-3-methanesulfonyloxy-4-pentenoate (**8**) (234 mg, 55%) as an oily mixture of diastereomers from the first fraction. IR ν_{max} (neat) cm^{-1}: 1720, 1690 (CO), 1350, 1145 (SO_2). The ^{1}H-NMR spectrum was not sufficiently well resolved to permit assignment of the signals. Selected ^{1}H-NMR data were as follows: δ ($CDCl_3$) 1.40 [$C(CH_3)_3$], 2.85 (OSO_2CH_3), 3.40, 3.50 (NCH_3 and/or $COOCH_3$), 4.35 (1-H), 5.4—5.7 (=CH_2, $CHOSO_2$), 6.35 (=CH), 7.1—7.5 (ArH). MS *m/z*: 492 (M^+). HRMS Calcd for $C_{24}H_{31}N_2O_7S$: 492.1927. Found: 492.1896. The second fraction eluted with 40% EtOAc in hexane gave **10** (42 mg, 14%), which was identical with an anthentic sample (**10**), based on comparison of their IR and ^{1}H-NMR spectra.

Synthesis of 12 (and 13) from 8 The mesylate (**8**) (234 mg, 0.48 mM) was dissolved in 2.3 N HCl/EtOAc (2 ml), and the mixture was stirred for 1 h. After removal of the solvent by evaporation, the residue was dissolved in DMSO (1 ml) containing DBU (80 mg, 0.53 mM). The mixture was allowed to stand for 3 h, diluted with water (10 ml), then extracted with EtOAc. The extract was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (40% EtOAc in hexane) to give **12** (77 mg, 54%) and **13** (9.2 mg, 6.5%), which were identical with an authentic samples (**12** and **13**), based on comparison of the IR and ^{1}H-NMR spectra.

Reaction of 7 with MsCl and TEA By a similar procedure to that described for the reaction of **6** with MsCl and TEA, a crude product was obtained from **7** (5.67 g, 12.8 mM), MsCl (1.48 ml, 19.2 mM), and TEA (5.39 ml, 38.4 mM). It was subjected to column chromatography. The first fraction eluted with 20% EtOAc in hexane gave methyl 2-(*tert*-butoxycarbonyl-9-methyl-1,2,3,4-tetrahydro-β-carbolin-1-yl)-3-methanesulfonyloxy-4-methylenehexanoate (**9**) (2.25 g, 34%) as a semi-solid. Recrystallization from EtOH gave colorless crystals, mp 155—157 °C. IR ν_{max} (Nujol) cm^{-1}: 1730, 1685 (CO), 1350, 1165 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.06 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.53 [9H, s, $C(CH_3)_3$], 1.97—2.24 (2H, m, $C\underline{H}_2CH_3$), 2.58 (3H, s, SCH_3), 2.66—2.87 (3H, m, 4'-H_2, 3'-H), 3.38 (3H, s, NCH_3), 3.50 (1H, dd, J=10.0, 5.0 Hz, CHCOO), 3.72 (3H, s, $COOCH_3$), 4.37 (1H, dd, J=14.0, 5.0 Hz, 2-H), 5.12, 5.32 (each 1H, each s, =CH_2), 5.63 (1H, d, J=10.0 Hz, $CHOSO_2$), 5.87 (1H, br d, J=4.0 Hz, ArCH), 7.16 (3H, m, ArH), 7.43 (1H, d, J=7.5 Hz, 8-H). MS *m/z*: 520 (M^+). *Anal.* Calcd for $C_{26}H_{36}N_2O_7S$: C, 59.98; H, 6.97; N, 5.38. Found: C, 59.95; H, 6.98; N, 5.45. The second fraction eluted with 40% EtOAc in hexane gave 2-(1-buten-1-yl)-1-methoxycarbonyl-12-methyl-1,6,7,12b-tetrahydro-2*H*,4*H*-indolo[2,3-*c*]pyrido[1,2-*c*][1,3]-oxazin-2-one (**11**) (498 mg, 11%). Recrystallization from EtOH gave colorless crystals, mp 173—174 °C. IR ν_{max} (Nujol) cm^{-1}: 1720, 1680 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.96—2.29 (2H, m, $C\underline{H}_2CH_3$), 2.70—3.05 (3H, m, 6-H and 7-H_2), 3.30 (3H, s, NCH_3), 3.47 (1H, dd, J=4.5, 2.5 Hz, 1-H), 3.64 (3H, s, $COOCH_3$), 4.73 (1H, m, 6-H), 5.05 (2H, br s, 12b-H, 2-H), 5.20, 5.27 (each 1H, each s, =CH_2), 7.17 (3H, m, ArH), 7.49 (1H, d, J=7.5 Hz, 11-H). MS *m/z*: 368 (M^+). *Anal.* Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.38; H, 6.55; N, 7.54.

***cis*-Methyl 2-(1-Buten-2-yl)-10-methyl-1,4,5,10b-tetrahydro-2*H*-azeto-[1',2':1,2]pyrido[3,4-*b*]indole-1-carboxylate (14)** By a similar procedure to that described for the preparation of **12** (and **13**), a crude product was obtained from **9** (539 mg, 1 mM). It was purified by column chromatography (40% EtOAc in hexane) to give **14** (139 mg, 43%). Recrystalization from EtOH gave colorless crystals, mp 132—134 °C. IR ν_{max} (Nujol) cm^{-1}: 1720 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.0 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.70—2.12 (2H, m, $C\underline{H}_2CH_3$), 2.66—3.11 (4H, m, CH_2×2), 3.20 (1H, dd, J=7.5, 2.5 Hz, 1-H), 3.56 (3H, s, NCH_3), 3.72 (3H, s, $COOCH_3$), 4.27 (1H, d, J=7.5 Hz, 2-H), 5.0, 5.42 (each 1H, each s, =CH_2), 5.10 (1H, d, J=2.5 Hz, 12b-H), 7.1—7.34 (3H, m, ArH), 7.55 (1H, d, J=7.5 Hz, 9-H). MS *m/z*: 324 (M^+). *Anal.* Calcd for $C_{20}H_{24}N_2O_2$: C, 74.07; H, 7.46; N, 8.64. Found: C, 73.97; H, 7.46; N, 8.51.

2-Ethenyl-1-methoxycarbonyl-11-methyl-1,6,7,12b-tetrahydro-2*H*,4*H*-indolo[2,3-*c*]pyrido[1,2-*c*][1,3]oxazin-4-ones (15 and 16) A solution of **6** (1.17 g, 2.8 mM) in 2.3 N HCl in EtOAc solution (6.5 ml) was stirred at room temperature for 1 h. After removal of the solvent by evaporation, the residue was neutralized with saturated $NaHCO_3$ solution and extracted with EtOAt. The extract was washed with brine, dried over Na_2SO_4, and concentrated to give the de-Boc derivative (873 mg, 99%) of **6** as a viscous oil. A solution of the de-Boc derivative (873 mg, 2.78 mM) thus obtained and Im_2CO (541 mg, 3.34 mM) in benzene (6 ml) was refluxed for 1 h. The reaction mixture was diluted with EtOAc (20 m), washed with water, dried over Na_2SO_4, and concentrated. The residue was subjected to column chromatography (15% EtOAc in benzene) to give **15** (482 mg, 54%) from the first eluate. Recrystallization from EtOH gave colorless crystals, mp 167—169 °C. IR ν_{max} (Nujol) cm^{-1}: 1735, 1680 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.6—3.0 (3H, m, 7-H_2, 6-H), 3.10 (1H, t, J=5.6 Hz, 1-H), 3.53 (3H, s, NCH_3), 3.76 (3H, s, $COOCH_3$), 4.63 (1H, q, J=10.0 Hz, 6-H), 4.96 (1H, t, J=5.6 Hz, 2-H), 5.20 (1H, d, J=10.5 Hz, H⟩=⟨H H), 5.35 (1H, d, J=17.0 Hz, H⟩=⟨H H), 5.39 (1H, d, J=5.6 Hz, 12b-H), 5.72 (1H, ddd, J=17.0, 10.5, 5.6 Hz, =CH), 7.16 (3H, m, ArH), 7.49 (1H, d, J=7.5 Hz, 11-H). MS *m/z*: 340 (M^+). *Anal.* Calcd for $C_{19}H_{20}N_2O_4$: C, 67.04; H, 5.92; N, 8.23. Found: C, 66.74; H, 5.92; N, 8.13. The second eluate with the same solvent gave **16** (211 mg, 23%), which was recrystallized from EtOH to give colorless crystals, mp 198—200 °C. IR ν_{max} (Nujol) cm^{-1}: 1740, 1680 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.85 (3H, m, 7-H_2, 6-H), 3.26 (3H, s, NCH_3), 3.71 (3H, s, $COOCH_3$), 3.62 (1H, dd, J=5.8, 2.8 Hz, 1-H), 4.82 (1H, m, 6-H), 5.04 (1H, br s, 2-H), 5.23 (1H, d, J=5.8 Hz, 12b-H), 5.32 (1H, d, J=10.0 Hz, H⟩=⟨H H), 5.54 (1H, d, J=17.5 Hz, H⟩=⟨H H), 5.86 (1H, ddd, J=17.5, 10.0, 5.8 Hz, =CH), 7.17 (3H, m, ArH), 7.49 (1H, d, J=7.5 Hz, 11-H). MS *m/z*: 340 (M^+). *Anal.* Calcd for $C_{19}H_{20}N_2O_4$: C, 67.04; H, 5.92; N, 8.23. Found: C, 67.03; H, 5.98; N, 8.16.

Methyl 2-Ethyl-1-methoxycarbonyl-11-methyl-1,6,7,12b-tetrahydro-2*H*,4*H*-indolo[2,3-*c*]pyrido[1,2-*c*][1,3]oxazin-4-one (17) A solution of **16** (0.1 g, 0.29 mM) in EtOAc (20 ml) was hydrogenated under atmospheric pressure with 5% Pd–C (50 mg) for 3 h. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was purified by column chromatography (15% EtOAc in hexane) to give **17** (75 mg, 75%) as an oil. IR ν_{max} (neat) cm^{-1}: 1730, 1685 (CO). ^{1}H-NMR ($CDCl_3$) δ:1.09 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.5—1.9 (2H, m, $C\underline{H}_2CH_3$), 2.6—3.0 (3H, m, 7-H_2, 6-H), 3.30 (3H, s, NCH_3), 3.70 (3H, s, $COOCH_3$), 3.55 (1H, dd, J=5.3, 3.0 Hz, 1-H), 4.40 (1H, m, 2-H), 4.81 (1H, m, 6-H), 5.15 (1H, d, J=5.3 Hz, 12b-H), 7.1—7.3 (3H, m, ArH), 7.48 (1H, d, J=7.5 Hz, 11-H). MS *m/z*: 342 (M^+). HRMS Calcd for $C_{19}H_{22}N_2O_4$: 342.1578. Found: 342.1574.

Preparation of Indoloquinolizidines (18, 19, and 20). Methyl 12-Methyl-3,6,7,12b-tetrahydro-4*H*-indolo[2,3-*a*]quinolizine-1-carboxylate (18) and Methyl 12-Methyl-1,6,7,12b-tetrahydro-4*H*-indolo[2,3-*a*]quinolizine-1-carboxylates (19 and 20) A solution of **15** (204 mg, 0.6 mM) and DBU (100 mg, 0.66 mM) in DMSO (3 ml) was heated at 120 °C for 4 h. The reaction mixture was diluted with EtOAc (40 ml), washed with water and brine, dried over Na_2SO_4, and concentrated. Purification of the residue by column chromatography afforded **20** (6 mg, 3.4%) (less polar), **19** (24 mg, 14%) (intermediate polar) by elution with 50% EtOAc in hexane, and **18** (54 mg, 30%) (more polar) by elution with EtOAc. The spectral data were in fair agreement with the reported values.[12]

18: IR ν_{max} ($CHCl_3$) cm^{-1}: 1700 (CO). ^{1}H-NMR ($CDCl_3$) δ: 3.54 (3H, 3H, NCH_3), 3.81 (3H, s, $COOCH_3$), 5.33 (1H, s, 2-H), 7.0—7.35 (3H, m, ArH), 7.58 (1H, d, J=7.5 Hz, 11-H). MS *m/z*: 296 (M^+). HRMS Calcd for $C_{18}H_{20}N_2O_2$: 296.1523, Found: 296.1541.

19: IR ν_{max} ($CHCl_3$) cm^{-1}: 1720 (CO). ^{1}H-NMR ($CDCl_3$) δ: 3.48 (3H, s, NCH_3), 3.71 (3H, s, $COOCH_3$), 3.95 (1H, br d, J=17.5 Hz, 4-H_{ax}), 4.5 (1H, d, J=9.5 Hz, 12b-H), 5.70, 5.95 (each 1H, each br d, J=10.5 Hz, 2-H, 3-H), 7.1—7.3 (3H, m, ArH), 7.45 (1H, d, J=7.5 Hz, 11-H). MS *m/z*: 296 (M^+). HRMS Calcd for $C_{18}H_{20}N_2O_2$: 296.1523. Found: 296.1497.

TABLE III. Crystal Data for Two Isomeric Tetrahydro-3,5-oxazin-4-ones (**10** and **15**)

	10	**15**
Molecular formula	$C_{19}H_{20}N_2O_4$	$C_{19}H_{20}N_2O_4$
Molecular weight	340.379	340.379
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	*Pbca*
Cell constant (Å)		
a	9.235 (2)	13.594 (3)
b	23.328 (3)	8.768 (1)
c	7.799 (1)	28.402 (6)
Volume (Å^3)	1680.2 (5)	3342 (1)
Z	4	8
D_x (g·cm^{-3})	1.3456	1.3529

20: IR ν_{max} ($CHCl_3$) cm^{-1}: 2800—2750 (Bohlmann bands), 1720 (CO). ^{1}H-NMR ($CDCl_3$) δ: 3.26 (3H, s, NCH_3), 3.73 (3H, s, $COOCH_3$), 3.98 (1H, br s, 12b-H), 5.95, 6.03 (each 1H, each br d, J=10.5 Hz, 2-H, 3-H), 7.0—7.3 (3H, m, ArH), 7.46 (1H, d, J=7.5 Hz, 11-H). MS m/z: 296 (M^+). HRMS Calcd for $C_{18}H_{20}N_2O_2$: 296.1523. Found: 296.1536.

X-Ray Determinations of Compounds 10 and 15 A single crystal (colorless needles) of **10** or **15**, recrystallized from EtOH, was used for the X-ray studies. The crystal data are summarized in Table III. Unit-cell dimensions were determined on a Rigaku four-circle diffractometer using high-angle reflections (2θ) by empolying graphite-monochromated Cu K_α radiation and were refined by the least-squares method. A total of 1570 (**10**) or 2670 (**15**) independent reflections ($2\theta_{max} < 130°$) was measured using the ω–2θ scan mode and a scan rate of 4°/min. Both structures were solved by the direct method using the MULTAN program[14] and refined by the least-squares method to R=0.0895 (**10**) and 0.0745 (**15**).

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