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Lactams. XXII.[1] Preparation of the Enantiomers of 6-Ethoxy-3-ethyl-2,3,4,5-tetrahydro-4-pyridineacetic Acid Ethyl Ester

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The resolution of (±)-*trans*-1-benzyl-5-ethyl-2-oxo-4-piperidineacetic acid [(±)-**1**] was effected with (*R*)-(+)-α-phenylethylamine through formation of the diastereomeric salts (+)-**2** and (−)-**3**. Conversion of (+)-**1** into the (3*R*,4*R*)-(+)-enantiomer [(+)-**6**] of the title compound proceeded *via* a route involving debenzylation of (+)-**1** with Na in liquid NH_3, esterification of the resulting (+)-**4** to give (+)-**5**, and ethylation of (+)-**5** with triethyloxonium fluoroborate. A parallel sequence of reactions starting from (−)-**1** produced (−)-**6** through (−)-**4** and (−)-**5**.

Keywords——lactam acid optical resolution; (*R*)-α-phenylethylamine salt; sodium–liquid ammonia debenzylation; Fischer–Speier esterification; triethyloxonium fluoroborate lactam-*O*-ethylation; chiral lactim ether synthesis

The (±)-lactim ether **6** has been a common key intermediate for our racemic syntheses of the *Alangium* alkaloids[2] and structurally related indoloquinolizidine alkaloids[3] through the "lactim ether route".[4] With the aim of extending this route to cover chiral syntheses of the above alkaloids, we tried to prepare the enantiomers of **6** from those of a suitable synthetic precursor in the racemic series. This paper reports the optical resolution of the (±)-lactam acid **1**[5] and conversions of the resulting enantiomers into (+)- and (−)-**6** along this line.

Equimolar amounts of (±)-**1** and optically pure (*R*)-(+)-α-phenylethylamine were dissolved in EtOH, and evaporation of the solvent from the resulting solution left a mixture of the diastereomeric salts. On repeated recrystallizations of the mixture from benzene, the less soluble salt (−)-**3** was obtained in 30% yield in the optically pure state. On the other hand, concentration of the mother liquor of the first recrystallization gave the other diastereomeric salt (+)-**2**, which was repeatedly recrystallized from AcOEt (26% yield) for purification. The extremely high optical purity of both salts was confirmed by the attainment of constant optical activities as well as by the fact that these activities were the same as those of samples obtained from the mother liquors of the final recrystallizations. However, an additional check of diastereomeric purity by means of proton nuclear magnetic resonance (^1H-NMR) spectroscopy was unsuccessful since there were no significant differences in the chemical shifts of the main sharp signals (in $CDCl_3$) between the two salts (+)-**2** and (−)-**3**.

Treatment of (+)-**2** with aqueous NaOH, followed by removal of the amine component and subsequent acidification, produced (+)-**1** in 98% yield. Debenzylation of (+)-**1** with Na in liquid NH_3 was effected according to the previous procedure[5a] for (±)-**1**, and the *N*-unsubstituted product was isolated in 89% yield in the form of the lactam acid (+)-**4** (46%) and the lactam ester (+)-**5** (43%). Esterification of (+)-**4** by the previously reported Fischer–Speier method[6] at 10—12 °C for 20 h furnished (+)-**5** in 95% yield. On treatment with triethyloxonium fluoroborate at room temperature for 22 h, (+)-**5** gave the desired lactim ether (+)-**6**, $[\alpha]_D^{25}$ +83.2° (EtOH), in 84% yield. A parallel series of conversions starting with (−)-**3** and proceeding through (−)-**1** (98% yield), (−)-**4** [45% besides (−)-**5** (43%)], and (−)-

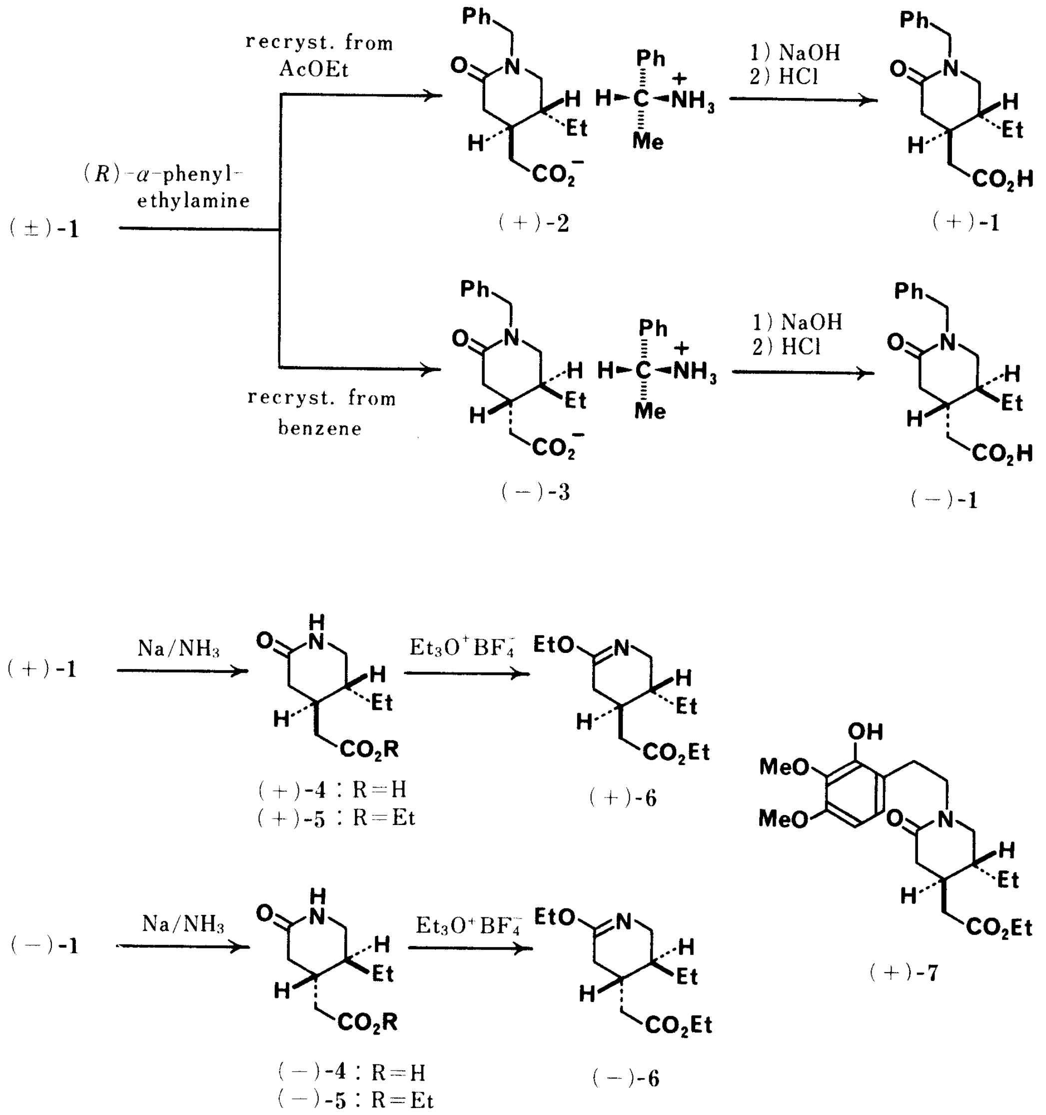

Chart 1

5 (96%), afforded the antipodal lactim ether (−)-6, $[\alpha]_D^{24}$ −83.7° (EtOH), in 86% yield from (−)-5.

The absolute stereochemistry of (+)-6 has been determined to be the same as that of known (+)-7 on the basis of chemical transformation of the former compound to the latter,[7] and the details of this conversion will be reported elsewhere in the near future. Consequently, all the chiral compounds obtained in the present study are represented by the absolute stereoformulas shown in Chart 1.

Experimental

General Notes——All melting points were determined with a Yamato MP-1 capillary melting point apparatus and are corrected; boiling points are uncorrected. Spectra reported herein were recorded on a JASCO A-202 infrared (IR) spectrophotometer, a Hitachi M-80 mass spectrometer, or a JEOL JNM-FX-100 NMR spectrometer, equipped with a ^{13}C FT NMR system, at 24 °C with Me_4Si as an internal standard. Optical rotations were measured with a JASCO DIP-181 polarimeter. Microanalyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, d = doublet, m = multiplet, q = quartet, s = singlet, t = triplet.

Resolution of (±)-*trans*-1-Benzyl-5-ethyl-2-oxo-4-piperidineacetic Acid [(±)-1]——A commercial sample of (*R*)-(+)-α-phenylethylamine was purified through formation of the (−)-malic acid salt according to the literature procedure,[8] giving a colorless oil, bp 81 °C (25 mmHg); $[\alpha]_D^{21}$ +40.1° (neat, $l=0.05$) [lit.[9] $[\alpha]_D^{25}$ +40.6° (neat)]. This purified amine (7.94 g, 65.5 mmol) was added dropwise to a solution of (±)-**1**[5] (18.04 g, 65.5 mmol) in EtOH (150 ml), and the mixture was concentrated to dryness *in vacuo*. The resulting colorless solid was recrystallized 12 times from benzene to afford pure (−)-**3** (3.92 g, 30%) as colorless fluffy needles, mp 125—126.5 °C; $[\alpha]_D^{20}$ −30.7° ($c=0.46$, EtOH); IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1705 (br) (carboxyl CO), 1628 (lactam CO); ^{1}H-NMR (CDCl$_3$) δ: 0.78 (3H, t, $J=7.1$ Hz, $\mathrm{CH_2\underline{Me}}$), 1.51 (3H, d, $J=6.8$ Hz, $\mathrm{CH\underline{Me}}$), 4.22 (1H, q, $J=6.8$ Hz, $\mathrm{\underline{C}HMe}$), 4.52 and 4.62 (2H, AB type d's, $J=15$ Hz, $\mathrm{\underline{CH_2}Ph}$), 6.69 (3H, s, $\mathrm{NH_3^+}$), 7.1—7.5 (10H, m, Ph's). *Anal.* Calcd for $\mathrm{C_{24}H_{32}N_2O_3}$: C, 72.70; H, 8.13; N, 7.06. Found: C, 72.40; H, 8.18; N, 6.97.

On the other hand, vacuum distillation of the solvent from the mother liquor of the above first recrystallization left a colorless solid. The solid was recrystallized 13 times from AcOEt to give pure (+)-**2** (3.35 g, 26%) as colorless fluffy needles, mp 134—135 °C; $[\alpha]_D^{22}$ +38.2° ($c=0.50$, EtOH); IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1700 (br) (carboxyl CO), 1625 (lactam CO); ^{1}H-NMR (CDCl$_3$) δ: 0.77 (3H, t, $J=7.1$ Hz, $\mathrm{CH_2\underline{Me}}$), 1.51 (3H, d, $J=6.8$ Hz, $\mathrm{CH\underline{Me}}$), 4.20 (1H, q, $J=6.8$ Hz, $\mathrm{\underline{C}HMe}$), 4.51 and 4.62 (2H, AB type d's, $J=15$ Hz, $\mathrm{\underline{CH_2}Ph}$), 6.88 (3H, s, $\mathrm{NH_3^+}$), 7.1—7.5 (10H, m, Ph's). *Anal.* Calcd for $\mathrm{C_{24}H_{32}N_2O_3}$: C, 72.70; H, 8.13; N, 7.06. Found: C, 72.85; H, 8.07; N, 7.26.

(4*R*, 5*R*)-(+)-1-Benzyl-5-ethyl-2-oxo-4-piperidineacetic Acid [(+)-1]——A solution of (+)-**2** (3.34 g, 8.4 mmol) in $\mathrm{H_2O}$ (40 ml) was made alkaline (pH 10) with 10% aqueous NaOH, washed with benzene, made acid to Congo red with 10% aqueous HCl, and extracted with $\mathrm{CHCl_3}$. The $\mathrm{CHCl_3}$ extracts were washed with saturated aqueous NaCl, dried over anhydrous $\mathrm{Na_2SO_4}$, and evaporated *in vacuo* to leave a colorless solid (2.27 g, 98%), mp 111.5—112.5 °C. Recrystallization of the solid from AcOEt provided (+)-**1** as colorless prisms, mp 113—114 °C; $[\alpha]_D^{21}$ +55.5° ($c=0.52$, EtOH); IR (CHCl$_3$) and ^{1}H-NMR (CDCl$_3$) identical with those of authentic (±)-**1**.[5] *Anal.* Calcd for $\mathrm{C_{16}H_{21}NO_3}$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.88; H, 7.80; N, 5.32.

(4*S*, 5*S*)-(−)-1-Benzyl-5-ethyl-2-oxo-4-piperidineacetic Acid [(−)-1]——This was prepared in 98% yield from (−)-**3** in a manner similar to that described above for (+)-**1**. Recrystallization of the acidic product from AcOEt yielded (−)-**1** as colorless prisms, mp 113—114 °C; $[\alpha]_D^{22}$ −55.9° ($c=0.52$, EtOH); IR (CHCl$_3$) and ^{1}H-NMR (CDCl$_3$) identical with those of authentic (±)-**1**.[5] *Anal.* Calcd for $\mathrm{C_{16}H_{21}NO_3}$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.55; H, 7.73; N, 5.14.

(4*R*, 5*R*)-(+)-5-Ethyl-2-oxo-4-piperidineacetic Acid [(+)-4]——To a stirred solution of (+)-**1** (4.63 g, 16.8 mmol) in liquid $\mathrm{NH_3}$ (400 ml) was added Na (1.17 g, 51 mg.-atom) in small pieces over a period of 1.5 h at the boiling point of liquid $\mathrm{NH_3}$. After the mixture had been stirred for 5 h, liquid $\mathrm{NH_3}$ (200 ml) was added. The resulting turbid mixture was stirred for an additional 3 h and then concentrated at room temperature to leave a colorless solid, which was dissolved in $\mathrm{H_2O}$ (35 ml). The aqueous solution was made acid to Congo red with concentrated aqueous HCl, washed with benzene without delay, and kept in a refrigerator overnight. The colorless precipitate that resulted was collected by filtration, washed with cold $\mathrm{H_2O}$, and dried to give (+)-**4** (1.42 g, 46%), mp 122—123.5 °C. Recrystallization from EtOH furnished an analytical sample as colorless prisms, mp 123—124 °C; $[\alpha]_D^{17}$ +82.7° ($c=0.49$, EtOH); IR $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1}: 3380 (NH), 1712 (CO$_2$H), 1634 (lactam CO); ^{1}H-NMR (Me$_2$SO-d_6) δ: 0.84 (3H, t, $J=6.8$ Hz, $\mathrm{CH_2\underline{Me}}$), 7.45 (1H, s, NH), 12.2 (1H, br, CO$_2$H); ^{13}C-NMR (Me$_2$SO-d_6) δ: 10.9 ($\mathrm{CH_2\underline{Me}}$), 23.1 ($\mathrm{\underline{C}H_2Me}$). *Anal.* Calcd for $\mathrm{C_9H_{15}NO_3}$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.22; H, 8.30; N, 7.35.

The aqueous filtrate and washings, which were obtained when crude (+)-**4** was isolated, were combined and concentrated to dryness *in vacuo*. The residue, after having been dried thoroughly in a desiccator, was stirred in 10% ethanolic HCl (25 ml) at 10—14 °C for 36 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in $\mathrm{H_2O}$ (20 ml). The aqueous solution was basified with $\mathrm{Na_2CO_3}$, salted out with $\mathrm{K_2CO_3}$, and extracted with benzene. The benzene extracts were dried over anhydrous $\mathrm{Na_2SO_4}$ and evaporated *in vacuo* to leave crude (+)-**5** (1.54 g, 43%) as a yellowish orange oil, $[\alpha]_D^{21}$ +61.7° ($c=0.54$, EtOH). The oil was identical [by comparison of thin-layer chromatographic (TLC) behavior and IR spectrum] with the sample of (+)-**5** described below.

(4*S*, 5*S*)-(−)-5-Ethyl-2-oxo-4-piperidineacetic Acid [(−)-4]——This was obtained from (−)-**1** in 45% yield according to a procedure similar to that described above for (+)-**4**. Recrystallization of crude (−)-**4** from EtOH yielded an analytical sample as colorless prisms, mp 123—124 °C; $[\alpha]_D^{18}$ −82.2° ($c=0.52$, EtOH); IR (Nujol), ^{1}H-NMR (Me$_2$SO-d_6), and ^{13}C-NMR (Me$_2$SO-d_6) identical with those of (+)-**4**. *Anal.* Calcd for $\mathrm{C_9H_{15}NO_3}$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.50; H, 8.16; N, 7.70. The aqueous filtrate and washings, which were obtained on isolation of crude (−)-**4**, were also worked up as described above for (+)-**4** and (+)-**5**, and crude (−)-**5** (43% yield) was isolated as a yellowish orange oil, $[\alpha]_D^{19}$ −65.4° ($c=0.50$, EtOH). The oil was identical (by comparison of TLC behavior and IR spectrum) with authentic (−)-**5**.

(4*R*, 5*R*)-(+)-5-Ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-5]——A solution of (+)-**4** (1.68 g, 9.1 mmol) in 10% ethanolic HCl (35 ml) was stirred at 10—12 °C for 20 h. The solution was concentrated *in vacuo*, and saturated aqueous NaCl (30 ml) was added to the residue. The resulting aqueous mixture was salted out with $\mathrm{K_2CO_3}$ and extracted with benzene. Drying over anhydrous $\mathrm{Na_2SO_4}$ and concentration *in vacuo* of the benzene extracts left (+)-**5** (1.83 g, 95%) as a pale yellowish oil, $[\alpha]_D^{14}$ +74.4° ($c=0.47$, EtOH); MS *m/e*: 213 (M$^+$); IR (CHCl$_3$), ^{1}H-NMR (CDCl$_3$), and TLC behavior identical with those of authentic (±)-**5**.[5a]

(4*S*, 5*S*)-(−)-5-Ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(−)-5]——The lactam acid (−)-**4** was esterified as described above for (+)-**5**, producing (−)-**5** (96% yield) as a pale yellowish oil, $[\alpha]_D^{14}$ −75.0° ($c=0.52$, EtOH); MS *m/e*: 213 (M^+). Apart from its optical activity, this sample was identical [by comparison of TLC behavior and IR ($CHCl_3$) and ^{1}H-NMR ($CDCl_3$) spectra] with authentic (±)-**5**.[5a)]

(3*R*,4*R*)-(+)-6-Ethoxy-3-ethyl-2,3,4,5-tetrahydro-4-pyridineacetic Acid Ethyl Ester [(+)-6]——A solution of triethyloxonium fluoroborate[10)] (2.1 g, 11 mmol) in dry CH_2Cl_2 (10 ml) was added dropwise to a stirred, ice-cooled solution of (+)-**5** (1.71 g, 8.0 mmol) in dry CH_2Cl_2 (10 ml) over a period of 20 min. The resulting mixture was stirred at room temperature for 22 h and then poured into cold 10% aqueous K_2CO_3 (20 ml). The precipitate that resulted was removed by filtration and washed with CH_2Cl_2, and the aqueous filtrate was extracted with CH_2Cl_2. The CH_2Cl_2 washings and extracts were united, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to leave an almost colorless oil. Vacuum distillation of the oil gave (+)-**6** (1.62 g, 84%) as a colorless oil, bp 103—104 °C (1 mmHg); $[\alpha]_D^{25}$ +83.2° (c=0.50, EtOH); MS *m/e*: 241 (M^+); IR (neat) and ^{1}H-NMR ($CDCl_3$) identical with those of authentic (±)-**6**.[2a)]

(3*S*,4*S*)-(−)-6-Ethoxy-3-ethyl-2,3,4,5-tetrahydro-4-pyridineacetic Acid Ethyl Ester [(−)-6]——This enantiomer was prepared from (−)-**5** in 86% yield according to the procedure described above for (+)-**6**. Distillation of crude (−)-**6** produced a pure sample as a colorless oil, bp 114 °C (2 mmHg); $[\alpha]_D^{24}$ −83.7° (c=0.61, EtOH); MS *m/e*: 241 (M^+); IR (neat) and ^{1}H-NMR ($CDCl_3$) identical with those of authentic (±)-**6**.[2a)]

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