Lactams. XII. Improvements in the Synthesis of Ethyl trans-5-Ethyl-2-oxo-4-piperidineacetate

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Lactams. XII.[1] Improvements in the Synthesis of Ethyl *trans*-5-Ethyl-2-oxo-4-piperidineacetate[2]

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A highly stereoselective, efficient synthetic route to ethyl *trans*-5-ethyl-2-oxo-4-piperidineacetate (**11a**) from 1-benzyl-2,4-dioxo-5-ethylpiperidine (**2**) is described. The steps involved are conversion of **2** into 1-benzyl-5-ethyl-2-oxo-1,2,5,6-tetrahydropyridine (**6**) through the lactam alcohol (**5**), the Michael condensation of **6** with diethyl malonate followed by alkaline hydrolysis, decarboxylation of the resulting *trans*-lactam dicarboxylic acid (**8a**) to the *trans*-lactam acid (**9a**), and debenzylation of **9a** followed by esterification.

Keywords——functionalized lactams; stereoselective synthesis; $NaBH_4$ reduction; dehydration; Michael addition; hydrolysis; decarboxylation; debenzylation; esterification

The 3-ethyl-4-piperidineacetic acid skeleton may be one of the most efficient, common key synthons conceivable for syntheses of a number of structurally related benzoquinolizidine and indoloquinolizidine alkaloids. In our recent synthesis of *dl*-emetine,[2,4] *dl*-ankorine,[4] *dl*-alangicine,[5] *dl*-dihydrocorynantheol,[6] and *dl*-dihydrocorynantheine,[6] we featured the introduction of an adequate phenethyl carbon skeleton onto the nitrogen of the title compound (**11a**),[7] the appropriate form of this important synthon, with the "lactim ether method"[8] developed newly. During the course of these alkaloid syntheses, the necessity of securing a substantial amount of the common intermediate **11a** provided the occasion for modifying our previous synthetic route[9,10] (**1**→**2**→**3**→**4**→**9a,b**→**10a,b**→**11a,b**).

1) Paper XI in this series, T. Fujii, M. Ohba, and S. Yoshifuji, *Chem. Pharm. Bull.* (Tokyo), **25**, 3042 (1977).
2) Presented in part at the 40th Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, Kanazawa, June 21, 1975.
3) Location: *13–1 Takara-machi, Kanazawa 920, Japan.*
4) T. Fujii, S. Yoshifuji, and K. Yamada, *Tetrahedron Lett.*, **1975**, 1527.
5) T. Fujii, K. Yamada, S. Yoshifuji, S. C. Pakrashi, and E. Ali, *Tetrahedron Lett.*, **1976**, 2553.
6) T. Fujii, S. Yoshifuji, and H. Ito, *Heterocycles*, **7**, 149 (1977).
7) T. Fujii, S. Yoshifuji, and M. Tai, *Chem. Pharm. Bull.* (Tokyo), **23**, 2094 (1975), and references cited.
8) T. Fujii, S. Yoshifuji, and K. Yamada, *Chem. Ind.* (London), **1975**, 177.
9) S. Sugasawa and T. Fujii, *Pharm. Bull.* (Tokyo), **3**, 47 (1955).
10) T. Fujii, *Chem. Pharm. Bull.* (Tokyo), **6**, 591 (1958).

Probably the most salient feature of the original route is that both the *trans*- (**9a**) and the *cis*-isomer (**9b**) can be easily obtained[7,9] in pure form by the hydrogenation (Pt/H_2, EtOH, 1 atm, 20°) of the unsaturated lactam acid **4**.[11] Although the stereoselectivity in this reduction is rather poor (**9a** : **9b**=58 : 42),[7] the *cis*→*trans* isomerization of the N-benzyl derivative (**9b**) or the debenzylated derivative (**10b**) under thermal or acid hydrolytic conditions[7] enables the overall stereochemical yield of the lactam ester **11a** to reach to an acceptable one. On the other hand, esterification of the cyanoacetic ester **3** (EtOH–HCl), followed by hydrolysis and decarboxylation with boiling aq. HCl, gives **4**[11] in only 34% yield.[9] Since the low yield in this step was the only major problem of our original scheme,[9,10] we first tried to improve it.

When **3** was heated in EtOH–conc. H_2SO_4 for 14 hr and the product was treated with boiling AcOH–aq. HCl for 15 hr, **4** was produced in 55% yield. Being unsatisfied with this result, we next examined an alternative, stereoselective route to **9a** from **2** (Chart 1), which was essentially the same as adopted by Battersby and Turner[12] for the N-(3,4-dimethoxyphenethyl) analog or by one (T. F.) of us for the debenzylated analog.[10]

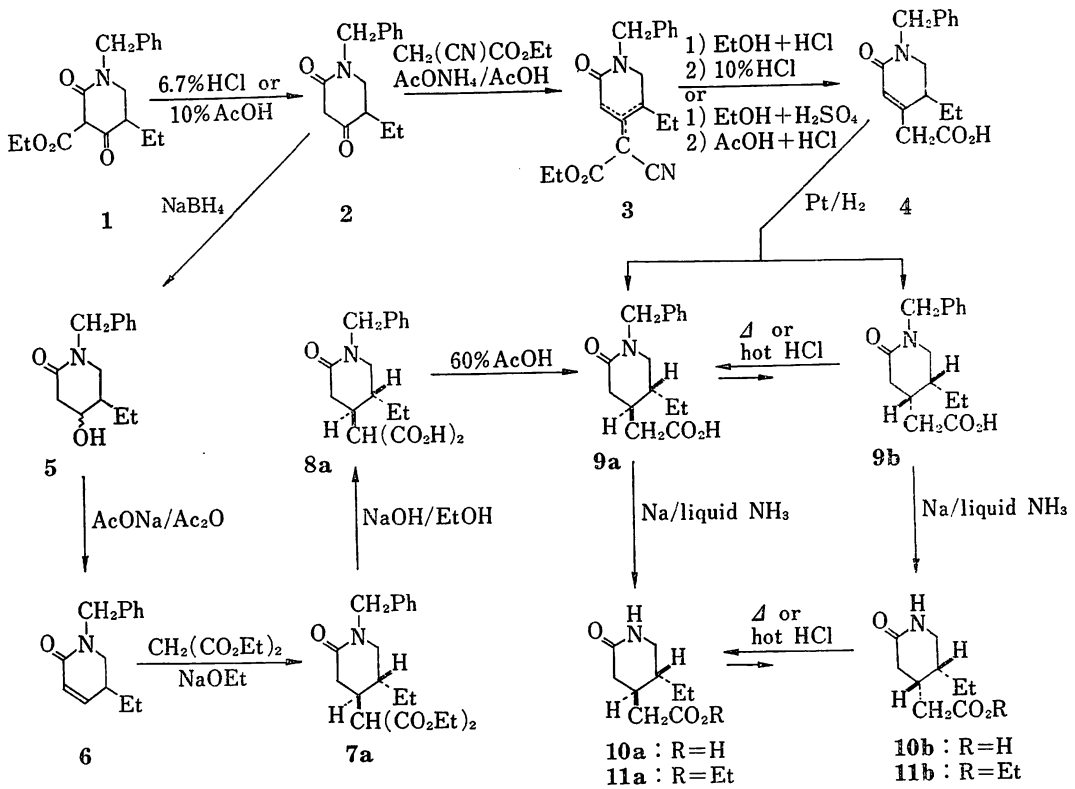


Chart 1

Thus, reduction of **2** with $NaBH_4$ in EtOH furnished the lactam alcohol **5** (99% yield) as an oil, presumed to be a diastereoisomeric mixture, which was dehydrated to the unsaturated lactam **6** (92% yield) by heating with Ac_2O–AcONa for 7 hr. The Michael addition

11) Although the location of the double bond in the acid **4**[9] has remained uncertain for a long time, our recent study (T. Fujii, H. Kogen, S. Yoshifuji, and K. Iga, Abstracts of Papers, 43rd Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, Kanazawa, November 20, 1976, p. 10) has established it as in structure **4**.

12) A. R. Battersby and J. C. Turner, *J. Chem. Soc.*, **1960**, 717.

of malonate anion to **6** and alkaline hydrolysis of the adduct **7a** provided the dicarboxylic acid **8a** (86% overall yield from **6**). By the analogy of the N-(3,4-dimethoxyphenethyl) analog[12] and related derivatives,[13] the major product was assigned the *trans* stereochemistry (**8a**). It was also supported by the noise-decoupled carbon-13 nuclear magnetic resonance (NMR) spectrum of **8a** in Me_2SO, which exhibited the methylene carbon signal of the ethyl group at 23.4 ppm (downfield from internal tetramethylsilane). This band position was close to that (22.5 ppm)[7] observed for the *trans*-acid **10a**, while far from that (19.4 ppm)[7] for the *cis*-acid **10b**. Decarboxylation of **8a** was effected in boiling 60% aq. AcOH for 6 hr to give the *trans*-acid **9a** (74% yield) as well as the *cis*-acid **9b** (4% yield). In a separate experiment, a precise ratio of both isomers (**9a** : **9b**=88 : 12), formed during the decarboxylation, was measured C-13 NMR spectroscopically as reported[7] before. The *trans*-acid **9a** was also transformed into the *cis*-isomer (**9b**) to the extent of 9% under the same reaction conditions. Although we are not certain whether the *trans*→*cis* isomerization occurs before and/or after the decarboxylation of **8a**, it seems to proceed through a mechanism similar to that proposed previously for the *cis*⇄*trans* isomerization of **9a,b** and **10a,b** in boiling 6 N aq. HCl. Debenzylation of **9a** was then effected with Na in liquid NH_3,[10,14] and the debenzylated product (85% yield) was isolated in the form of the lactam acid **10a** and the lactam ester **11a**. Esteri-fication of **10a** [HCl–EtOH (1: 9, w/w), 15°, 16 hr][15] afforded the desired compound (**11a**) in 96% yield.

The ketonic cleavage of the lactam keto ester **1** was originally carried out in boiling 6.7% aq. HCl for 3 hr, giving **2** in 84% yield.[9] In the present work, replacement of the mineral acid by boiling 10% aq. AcOH[16] could raise the yield of **2** to 98%. The success of this procedure is probably due to the milder acid conditions under which the lactam ring could be kept intact.

Yet another synthetic route to **11a,b** is that of Preobrazhensky *et al.*,[17] who converted diethyl glutaconate into **11a,b** by the Michael condensation with ethyl cyanoacetate followed by ethylation, selective saponification, decarboxylation, and reductive cyclization. In spite of the closer study of this route by van Tamelen *et al.*,[18] however, the poor overall yield of **11a,b** has not been improved. Thus, the present modification of our original route would be the choice of the method for preparation of the key intermediate (**11a**).

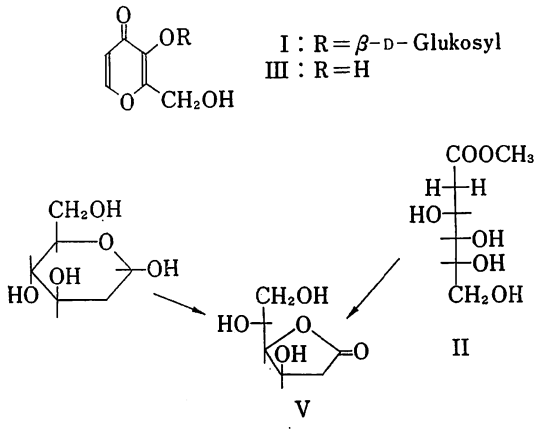
Experimental

All melting points are corrected; boiling points, uncorrected. See ref. 7 for details of instrumentation and measurement. The following abbreviations are used: b=broad, d=doublet, d-d=doublet-of-doublets, m=multiplet, s=singlet, t=triplet.

1-Benzyl-2,4-dioxo-5-ethylpiperidine (2)——A mixture of the lactam keto ester **1**[9] (196 g, 0.646 mol) and 10% (v/v) aq. AcOH (2 l) was refluxed for 4.5 hr. After cooling, the reaction mixture was extracted with benzene (3×500 ml). The combined extracts were washed successively with sat. aq. NaCl, sat. aq. $NaHCO_3$, and sat. aq. NaCl, dried over anhyd. Na_2SO_4, and evaporated to dryness *in vacuo*, leaving **2** (146 g, 98%) as a yellowish brown, fluorescent, viscous oil, identical [by comparison of infrared (IR) spectrum] with an authentic sample.[9] Rapid distillation of part (32.6 g) of the crude sample gave a colorless, viscous oil (29.4 g), bp 172—173° (1 mmHg); IR ν_{max}^{film} cm^{-1}: 1726 (CO), 1656 (lactam CO); NMR ($CDCl_3$) δ: 0.82 (3H, t, J=7 Hz, $CH_2\underline{CH_3}$), 1.04—1.98 (2H, m, $C\underline{H_2}CH_3$), 2.2—2.54 (1H, m, $H_{(5)}$), 3.1—3.62 (2H, m, $H_{(6)}$'s), 3.40 (2H, s, $H_{(2)}$'s), 4.68 (2H, s, $C\underline{H_2}C_6H_5$), 7.35 (5H, s, C_6H_5).

13) T. Fujii, S. Yoshifuji, and K. Ikeda, *Heterocycles*, **5**, 183 (1976), and references cited.
14) S. Sugasawa and T. Fujii, *Chem. Pharm. Bull.* (Tokyo), **6**, 587 (1958).
15) We have confirmed by means of C-13 NMR spectroscopy[7] that the *trans*→*cis* or the *cis*→*trans* isomerization of **10a** or **10b** did not occur at all under these esterification conditions, but the same esterification at 32° (16 hr) or at reflux gave a mixture of both isomeric esters (**11a, b**). The details will be published elsewhere shortly.
16) Patterned after the procedure of Y. Ban, *Pharm. Bull.* (Tokyo), **3**, 53 (1955).
17) R. P. Evstigneeva and N. A. Preobrazhensky, *Tetrahedron*, **4**, 223 (1958), and references cited.
18) E. E. van Tamelen and J. B. Hester, Jr., *J. Am. Chem. Soc.*, **91**, 7342 (1969).

Im NMR-Spektrum von II' finden sich ein Dublett (2H, J=7 Hz) bei δ 2.55 für die einem Ester benachbarten Methylenprotonen und ein Singulett (3H) bei δ 3.67 für die Methylesterprotonen. Im sonstigen Bereich ist das Spektrum mit demjenigen der peracetylierten 2-Deoxy-D-glukose (IV) identisch und das enthält zwei Multiplette, d.h., eins (2H) zwischen δ 4.1 und 4.3 für die Methylenprotonen am C-6 von IV sowie ein anderes (3H) zwischen δ 5.0 und 5.7 für die Methinprotonen am C-3, C-4 und C-5 von IV. Diese und Infrarot (IR)-Daten, u.a., eine Estercarbonyl-Bande bei 1720 cm^{-1} deuten darauf hin, dass es sich bei II um 2-Deoxy-D-glukonsäure-methylester handelt. Durch Hydrolyse mit Alkali ergab II ein öliges γ-Lakton (V) von $[\alpha]_D^{17}$ +27.8°(c=1.21, MeOH), das durch Vergleich mit dem synthetischen Material[5] aus 2-Deoxy-D-glukose identifiziert wurde. Demnach kommt der Substanz II die Struktur eines 2-Deoxy-D-glukonsäuremethylester zu.



Die oberirdischen Teile von *Pteris formosana* BAKER, die im Dezember 1974 in Kukuan, Taiwan, China gesammelt wurden, enthielten ebenfalls das Glykosid I neben 2-Deoxy-D-glukose, 3,6-Anhydro-2-deoxy-D-glukose und Pterosin B[6] sowie Pterosin Z.[7]

Experimenteller Teil

Die UV-Spektren wurden mit einem Hitachi-Spektrophotometer EPS-3A, die IR-Spektren mit einem Hitachi-Spektrophotometer Model 215, die NMR-Spektren mit einem Nihon-Denshi-Spektrometer JNM-4H-100 aufgenommen. Zur Aufnahme der Massenspektren diente ein Hitachi-Massenspektrometer RMU-7M mit Direkteinlasssystem.

Isolierung der Inhaltsstoffe——Die lufttrockenen Pflanzenteile extrahierte man unter Rückfluss mit MeOH. Die erhaltenen Extrakte wurden im Vakum eingedampft und der Rückstand in 50% MeOH suspendiert und mit Äther geschüttelt. Die MeOH–H_2O–Phase wurde eingedampft und den Rückstand trennte man zunächst durch Säulenchromatographie (Kieselgel) mit $CHCl_3$ bei zunehmendem MeOH-Zusatz. Die mit $CHCl_3$–MeOH (8:2) eluierten Fraktionen wurden durch präparative Dünnschichtchromatographie (DC) (Kieselgel GF-254, Laufmittel: $CH_3COOC_2H_5$, dreimaliges Lauflassen) getrennt. 2 kg oberirdische Teile von *P. inaequalis* BAKER var. *aequata* (MIQ.) TAGAWA, die im Juli 1974 in Satsuma-Oguchi/Kagoshima-Präfektur gesammelt wurden, ergaben 130 mg von I und 170 mg von II. 1 kg oberirdische Teile von *P. formosana* BAKER lieferten 85 mg von I.

Glykosid I——Farblose Nadeln vom Schmp. 148° (aus MeOH). $C_{12}H_{16}O_9$, Ber, C, 47.37; H, 5.30. Gef C, 46.99; H, 5.37. UV: λ_{max}^{MeOH} nm (log ε) 260 (3.86), IR: ν_{max}^{KBr} cm^{-1} 3350, 1642, 1600, NMR (in CD_3OD): δ 6.6((1H, d, J=6 Hz), 8.13 (1H, d, J=6 Hz). Pentaacetat (I'): Farblose Nadeln vom Schmp. 120° (aus MeOH), $C_{22}H_{26}O_{14}$, Ber. C, 51.36; H, 5.09. Gef. C, 51.05; H, 5.41. UV: λ_{max}^{MeOH} nm (log ε) 260 (3.86), IR: ν_{max}^{KBr} cm^{-1} 1740, 1645, NMR (in $CDCl_3$): δ 2.02—2.12 (15H), 3.7 (1H, m), 4.15 (2H, m), 5.10 (2H, s), 5.2—5.35 (3H, m), 6.38 (1H, d, J=6 Hz), 7.68 (1H, d, J=6 Hz), MS: m/e 184, 331, 271, 211, 169, 109.

Hydrolyse von I——Die Hydrolyse erfolgte mit β-Glukosidase in Acetat-Puffer-Lösung (pH 5.6) (40 Stdn, bei 37°). Das nach Abtrennen der β-Glukosidase und Eindampfen erhaltene Hydrolyseprodukt wurde durch präparative DC mit $CHCl_3$/MeOH (5:1) gereinigt. III (Hydroxymaltol): Farblose Nadeln vom Schmp. 155° (aus MeOH). $C_6H_6O_4$ (M^+: 142.0266). UV: λ_{max}^{MeOH} nm (log ε) 268 (4.20). IR: ν_{max}^{KBr} cm^{-1} 3300, 1645, 1610. NMR (in CD_3OD): δ 4.6 (2H, s), 6.4 (1H, d, J=6 Hz), 8.0 (1H, d, J=6 Hz).

Substanz II——Farblose Nadeln vom Schmp. 145° (aus MeOH). $C_7H_{14}O_6$ (M^++1: 195). Ber. C, 43.29; H, 7.27. Gef. C, 43.20; H, 7.10. IR: ν_{max}^{KBr} cm^{-1} 3300, 1720. NMR (in CD_3OD): δ 2.55 (2H, d, J=7 Hz), 3.67 (3H, s). MS m/e: 195, 163, 145, 127. Tetraacetat (II'): Farblose Nadeln vom Schmp. 62° (aus MeOH). $C_{15}H_{22}O_{10}$, Ber. C, 49.72; H, 6.12. Gef. C, 49.52; H, 6.00. NMR (in $CDCl_3$): δ 2.0—2.15

5) M. Bergmann, H. Schotte, und W. Leschinsky, *Chem. Ber.*, **56**, 1053 (1923).
6) M. Kuroyanagi, M. Fukuoka, K. Yoshihira, und S. Natori, *Chem. Pharm. Bull.* (Tokyo), **22**, 2762 (1974).
7) K. Yoshihira, M. Fukuoka, M. Kuroyanagi, und S. Natori, *Chem. Pharm. Bull.* (Tokyo), **19**, 1491 (1971).

from AcOEt–hexane (1 : 1, v/v) (2 : 1, v/v) gave colorless prisms (2.64 g, 4%), mp 100—102°, identified with authentic *cis*-lactam acid **9b**.[7]

In a separate experiment, an analytically pure sample (120 mg, 0.37 mmol) of **8a** was heated under reflux for 6 hr with 60% (v/v) aq. AcOH (2.4 ml). The solvent was removed by vacuum distillation to afford a colorless solid, which was dried and dissolved in $CDCl_3$ (2 ml). Analysis of the $CDCl_3$ solution by means of ^{13}C FT NMR spectroscopy[7] revealed that it contained an 88 : 12 mixture of **9a** and **9b**.

In yet another experiment, a pure sample of **9a** was treated in the same way as described above for **8a**, and the material recovered from the reaction mixture was analyzed in the same way, disclosing that it was a 91 : 9 mixture of **9a** and **9b**.

***trans*-5-Ethyl-2-oxo-4-piperidineacetic Acid (10a)**——To a stirred solution of **9a** (5.51 g, 20 mmol) in liquid NH_3 (250 ml) was added in small pieces Na (1.38 g, 60 mg.-atom) over a period of 1.5 hr. After the mixture was stirred without any external cooling for 2 hr, liquid NH_3 (400 ml) was added. The resulting turbid mixture was further stirred in the same manner until it was freed from the liquid. The residual, colorless solid was dissolved in H_2O (30 ml), and the aqueous solution, after having been made acid to Congo red with conc. aq. HCl (*ca.* 6 ml), was extracted with benzene (2 × 100 ml) without delay. From these benzene extracts, the starting N-benzyl derivative (**9a**) (284 mg, 5.2%), mp 106—108°, was recovered. The aqueous solution that remained was kept in a refrigerator overnight, and the colorless needles that resulted were filtered off, washed with cold H_2O (3 × 3 ml), and dried to give **10a** (2.08 g, 56%), mp 146—148°, identified (by mixed melting-point test and comparison of IR spectrum) with an authentic sample.[7,10] The aqueous filtrate and washings were combined and evaporated *in vacuo* to dryness. The residue, after having been dried thoroughly in a desiccator, was stirred in 10% ethanolic HCl (25 ml) at 15° (bath temp.) for 24 hr. The EtOH was evaporated *in vacuo*, and H_2O (20 ml) was added to the residue. The aqueous solution was basified with Na_2CO_3, salted out with K_2CO_3, and extracted with benzene (3 × 20 ml). The combined benzene extracts were dried over anhyd. Na_2SO_4 and evaporated to leave a yellowish orange solid, mp 78—90°. Recrystallization of the solid from isopropyl ether furnished **11a** (1.23 g, 29% yield from **9a**) as colorless pillars, mp 93.5—94.5°, identical (by mixed melting-point test and comparison of IR spectrum) with an authentic sample.[7,10] The total yield of the debenzylated products (**10a, 11a**) was 85%.

Ethyl *trans*-5-Ethyl-2-oxo-4-piperidineacetate (11a)——A solution of **10a** (222 mg, 1.2 mmol) in 10% ethanolic HCl (12 ml) was kept at 15° (bath temp.) for 16 hr. The solution was evaporated *in vacuo*, and sat. aq. $NaHCO_3$ (10 ml) was added to the residue. The resulting mixture was extracted with $CHCl_3$ (1 × 20 ml, 2 × 10 ml), and the combined extracts were washed with sat. aq. NaCl (15 ml) and dried over anhyd. Na_2SO_4. Evaporation of the solvent left **11a** (246 mg, 96%) as colorless pillars, mp 92—94°, identical (by mixed melting-point test and IR spectroscopy) with an authentic sample.[7,10]

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