

WITTIG REACTIONS OF 1-ALKOXYCARBONYL-2-HYDROXYPYRROLIDINES AND
-PIPERIDINES: SYNTHESSES OF (±)-HYGRINE AND (±)-2-EPIIASUBINE II

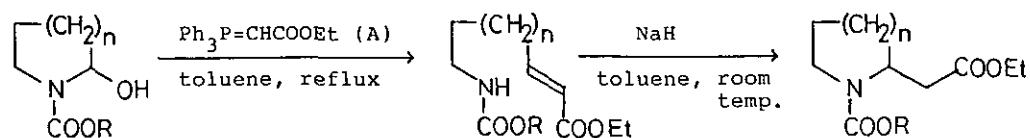
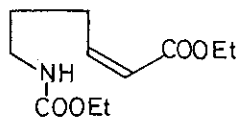
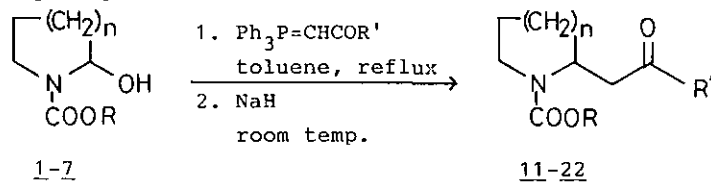
Tatsuo Nagasaka,* Hiroto Yamamoto, Hideki Hayashi,
Mariko Watanabe, and Fumiko Hamaguchi
Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji,
Tokyo 192-03, Japan

Abstract — One-pot reactions of 1-alkoxycarbonyl-2-hydroxypyrrolidines and -piperidines with Wittig reagents stabilized by carbonyl groups give α -alkylated pyrrolidines and piperidines in good yields. The syntheses of (±)-hygrine and (±)-2-epilasubine II using the Wittig products are described.

Reactions for introducing functional groups at the α -position of cyclic amines are currently of great interest,¹ in view of the many such derivatives as alkaloids, antibiotics and medicines consisting of the α -substituted cyclic amine structures that have been obtained in this way. In our previous paper,² we reported that reactions of 1-ethoxycarbonyl-2-hydroxypyrrolidine 2, readily obtainable from 2-pyrrolidinone in three steps,³ with carbonyl compounds in the presence of a base give α -alkylated pyrrolidines in moderate to high yields. In the present study, reactions of 2-hydroxycarbamates (1-7) with Wittig reagents stabilized by carbonyl groups were carried out as an alternative means for introducing carbon-functional groups at the α -position of cyclic amines.⁴ The results of applying this method to the alkaloid syntheses of (±)-hygrine and (±)-2-epilasubine II are presented.

A detailed study was first made of the reaction of hydroxycarbamate 2 with ethyl triphenylphosphonoacetate (A) to give mainly the unsaturated ester 8. The following solvents were used (reaction conditions and yield of 8 are indicated in parenthesis): 1) dichloromethane (reflux, 24 h; 0%), 2) dimethyl sulfoxide (room temperature, 4 h; 10.5%), 3) dimethoxyethane (reflux, 12 h; 65.4%), 4) toluene (reflux, 1.5 h; 80.3%). The products, obtained by refluxing in toluene, were separated by chromatography into E-isomer 8 and Z-isomer 10 in 80.3% and 4.7% yields, respectively. A similar reaction of six-membered hydroxycarbamate 5 was

Scheme 1

1 n=1, R=Me8 n=1, R=Et (80.3%)11 n=1, R=Et (78.3%)2 n=1, R=Et9 n=2, R=Me (70.9%)12 n=2, R=Me (87.2%)3 n=1, R=CH₂CH=CH₂4 n=1, R=l-menthyl5 n=2, R=Me6 n=2, R=CH₂CH=CH₂7 n=2, R=l-menthyl10 (4.7%)Table I. One-Pot Reactions of 2-Hydroxycarbamates (1-7) with Stabilized Wittig Reagents (A-D)

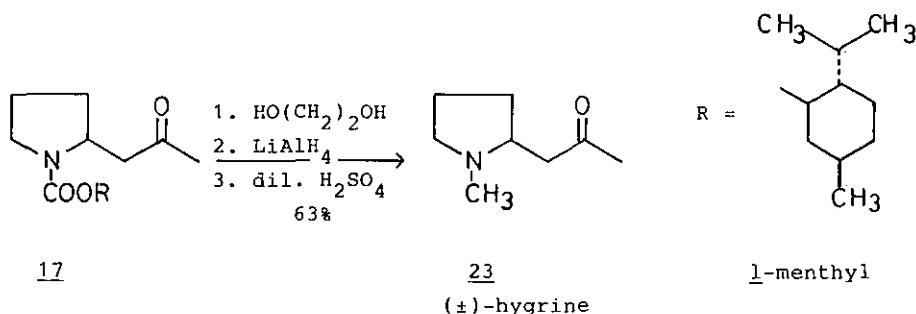
Run	2-Hydroxycarbamates	Ph ₃ P=CHCOR' [*]	Products (<u>11-22</u>)	Isolated Yield (%)
1	<u>2</u>	A	<u>11</u> : n=1, R=Et, R'=OEt	76.0
2	<u>2</u>	C	<u>13</u> : n=1, R=Et, R'=Me	74.5
3	<u>1</u>	D	<u>14</u> : n=1, R=Me, R'=CH=CHPh	69.0
4	<u>3</u>	A	<u>15</u> : n=1, R=CH ₂ CH=CH ₂ , R'=OEt	86.1
5	<u>4</u>	B	<u>16</u> : n=1, R= <u>l</u> -menthyl, R'=OMe	87.4
6	<u>4</u>	C	<u>17</u> : n=1, R= <u>l</u> -menthyl, R'=Me	90.9
7	<u>5</u>	A	<u>12</u> : n=2, R=Me, R'=OEt	51.5
8	<u>5</u>	C	<u>18</u> : n=2, R=R'=Me	43.3
9	<u>6</u>	C	<u>19</u> : n=2, R=CH ₂ CH=CH ₂ , R'=Me	27.4
10	<u>6</u>	B	<u>20</u> : n=2, R=CH ₂ CH=CH ₂ , R'=OMe	55.4
11	<u>7</u>	C	<u>21</u> : n=2, R= <u>l</u> -menthyl, R'=Me	67.0
12	<u>5</u>	D	<u>22</u> : n=2, R=Me, R'=CH=CH ^t Ph	6.6

* A: R'=OEt, B: R'=OMe, C: R'=Me, D: R'=trans-CH=CHPh

then carried out to afford the unsaturated ester 9 in good yield (70.9%).⁵ The intramolecular Micheal addition of these unsaturated esters 8 and 9 was successfully carried out by stirring them with equivalent quantities of sodium hydride in toluene at room temperature to give cyclic amines 11 and 12 in 78.3% and 87.2% yields, respectively. In consideration of the above results, the conversion of hydroxyurethanes 2 and 5 to cyclic amines 11 and 12 was carried out in one-pot by refluxing 2 and 5 with a Wittig reagent in toluene followed by the addition of sodium hydride,⁶ giving 11 and 12 in 76% and 51.5% overall yields, respectively. The results by one-pot Wittig reactions of 1-alkoxycarbonyl-2-hydroxypyrrolidines (1-4) and -piperidines (5-7) are summarized in Table I. Generally, the yields of the pyrrolidine derivatives (11, 13-17) were high, with those of piperidine derivatives (12, 18-22) being moderate to low. This appeared to depend on hydroxycarbamate stability, the hydroxycarbamates of pyrrolidine (1-4) being more stable than those of piperidine (5-7)^{2,7}

Compound 17, having a chiral group at the N-position and whose separation into diastereomers was expected,^{8,9} was converted to hygrine 23 following a method in the literature,¹⁰ (Scheme 2). The ketalization of 17 and subsequent reduction with lithium aluminum hydride and hydrolysis with aqueous sulfuric acid afforded racemic hygrine 23 in 63% overall yield. No diastereomer at the 2-position of pyrrolidine ring of 17 or other intermediates could be separated.

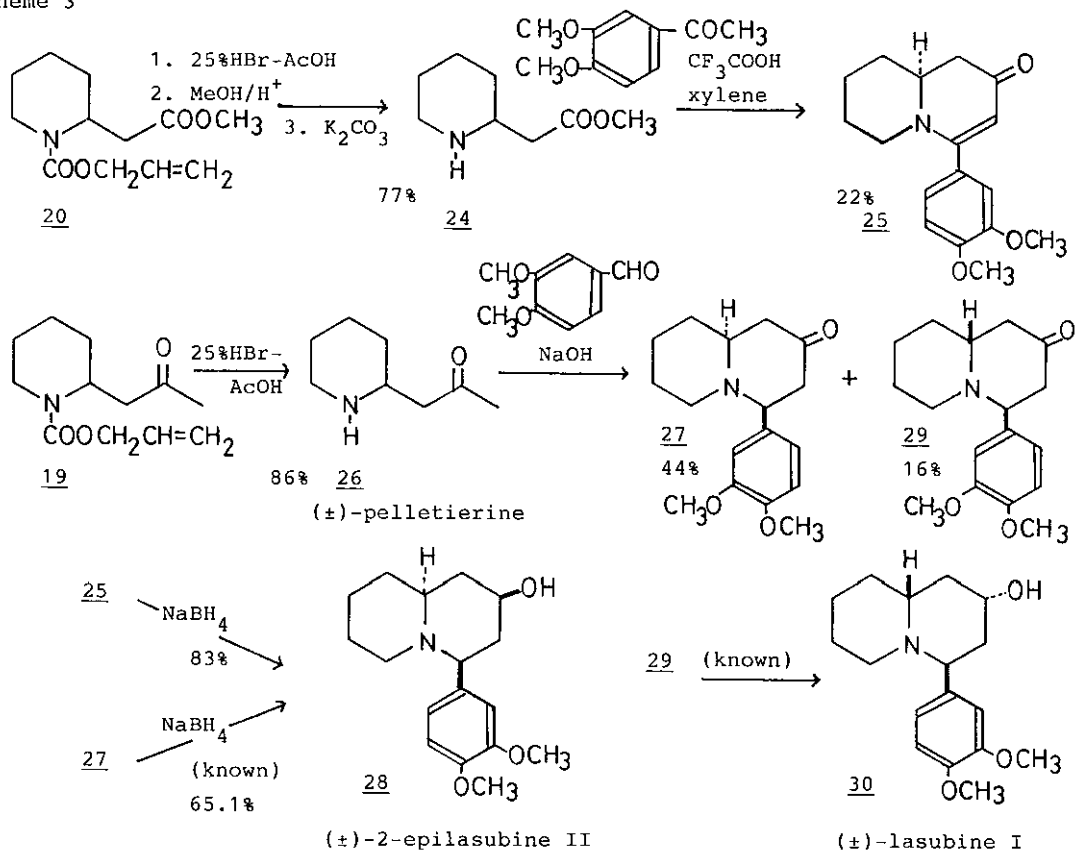
Scheme 2



(±)-Epilasubine II 28 was synthesized using Wittig products 19 and 20. Carbamate 20 was hydrolyzed by 25% hydrobromic acid in acetic acid¹¹ to amine 24 in 77% yield, which, without purification, was refluxed with 3,4-dimethoxyacetophenone in xylene in the presence of trifluoroacetic acid to give quinolizidinone 25 in 22% yield. The reduction of 25 with sodium borohydride in ethanol gave (±)-2-epilasubine II 28 as a single product in 83% yield (Scheme 3). The reaction of carbamate 19 with 25% hydrobromic acid in acetic acid produced (±)-pelletierine 26 in 86%

yield. This compound has been used for the syntheses of (+)-lasubine I 30 and (+)-2-epilasubine II 28.¹² Following the method,¹² pelletierine 26 was condensed with veratraldehyde in the presence of a base to give *trans*-quinolizidinone 27 and *cis*-quinolizidinone 29 in 44% and 16% yields, respectively.¹³ The reduction of 27 with sodium borohydride gave (+)-2-epilasubine II 28 in 65% yield; it was identical with the sample obtained from 20 as described before. Synthesis of (+)-lasubine I 30 from *cis*-quinolizidinone 29 has been reported.¹²

Scheme 3



Based on the data presented above, the reactions of 2-hydroxycarbamates with the Wittig reagent stabilized by carbonyl groups may be concluded to serve as a means for obtaining α -alkylated pyrrolidine and piperidine derivatives by which alkaloid syntheses can be effectively carried out. This method is applicable to the transformation of commercially available lactams into α -alkylated cyclic amines.

EXPERIMENTAL

All melting points were determined by micro-melting point apparatus (Yanagimoto) without correction. Ir and mass spectra were measured on Hitachi 200-10 and Hitachi M-80 spectrometers, respectively. $^1\text{H-Nmr}$ spectra were recorded on a Varian EM-390 instrument. Chemical shifts were recorded in ppm downfield from an internal standard (tetramethylsilane). The following abbreviations were used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. Chromatographic separations were made using a silica gel (Wako-gel C-200) column. Thin-layer chromatography (tlc) was carried out with pre-coated silica gel plates (Kiesel 60 F-254, Merck). The physical properties and elemental analyses of Wittig products (8-22 except 13) are listed in Tables II and III, respectively. The physical data of compound 13 are presented in our previous paper.²

2-Hydroxycarbamate (1-7) -- Hydroxycarbamates (1-7) were prepared by the acidic hydrolysis² of the corresponding 2-ethoxycarbamates.³ Their elemental analyses, except that of compound 4, failed to provide satisfactory data owing to instability during distillation. But their mass spectra showed the same fragment pattern (M^+-OH). The physical properties of compounds 2 and 3 are given in the previous paper². 1: oil (quant. yield), ir (neat) 3410, 1700 cm^{-1} , $^1\text{H-nmr}$ (CDCl_3) δ 1.81 (m, 4H, $\text{CH}_2 \times 2$), 3.04-3.61 (m, 3H, NCH_2 , CHOH), 3.74 (s, 3H, OCH_3), 5.41-5.61 (m, 1H, NCHOH). 4: oil (78%), ir (CHCl_3) 3450, 1700 cm^{-1} , $^1\text{H-nmr}$ (CDCl_3) δ 0.78 (d, $J=7.5\text{Hz}$, 3H, CHCH_3), 0.89 (d, $J=7.5\text{Hz}$, 6H, $\text{CH}(\text{CH}_3)_2$), 1.07-2.07 (m, 13H, $\text{CH}_2 \times 5$, $\text{CH} \times 3$), 3.10-3.67 (m, 2H, NCH_2), 4.00 (br, 1H, OH), 4.40-4.78 (m, 1H, CHOCO), 5.33-5.56 (m, 1H, NCHOH). Anal. Calcd for $\text{C}_{15}\text{H}_{27}\text{NO}_3$: C, 66.88; H, 10.10; N, 5.17. Found: C, 67.10; H, 10.24; N, 5.17. 5: oil (93%), ir (neat) 3440, 1680 cm^{-1} , $^1\text{H-nmr}$ (CDCl_3) δ 1.37-2.17 (m, 6H, $\text{CH}_2 \times 3$), 2.92-3.47 (m, 1H, HCHN), 3.68 (s, 3H, OCH_3), 3.70-4.03 (m, 2H, HCHN , OH), 5.60-5.83 (m, 1H, OCHN). 6: oil (quant. yield), ir (neat) 3440, 1680 cm^{-1} , $^1\text{H-nmr}$ (CDCl_3) δ 1.38-2.22 (m, 6H, $\text{CH}_2 \times 2$), 2.92-3.52 (m, 1H, HCHN), 3.68-4.05 (m, 2H, HCHN , OH), 4.47-4.75 (m, 2H, OCH_2CH), 5.08-5.55 (m, 2H, $\text{CH}=\text{CH}_2$), 5.65-6.22 (m, 2H, $\text{CH}_2\text{CH}=\text{CH}_2$, NCHO). 7: oil (64.6%), ir (neat) 3400, 1670 cm^{-1} , $^1\text{H-nmr}$ (CDCl_3) δ 0.78 (d, $J=7\text{Hz}$, 3H, CHCH_3), 0.88 (d, $J=7\text{Hz}$, 6H, $\text{CH}(\text{CH}_3)_2$), 1.35-2.45 (m, 15H, $\text{CH}_2 \times 6$, $\text{CH} \times 3$), 2.78-3.33 (m, 1H, HCHN), 3.67-4.02 (m, 1H, HCHN), 4.35-4.78 (m, 1H, CHOCO), 5.62-5.85 (m, 1H, NCHOH).

Ethyl (E and Z)-6-Ethoxycarbonylamino-2-hexenoate (8 and 10) -- A mixture of hydroxycarbamate 2 (954 mg, 6 mmol) and phosphonoacetate (A) (2.09 g, 6 mmol) in toluene (50 ml) was refluxed for 2.5 h under an Ar atmosphere followed by evaporation to give a semisolid, which, on chromatographic separation by elution with benzene-acetone (20:1), afforded 65 mg (4.7%) of 10 from the first crop and 1.103 g (80.3%) of 8 from the second.

Ethyl (E)-7-Methoxycarbonylamino-2-heptenoate (9)⁵ -- In accordance with the method presented above, 324 mg (70.7%) of 9 were obtained by refluxing hydroxycarbamate 5 (318 mg, 2 mmol) and phosphonoacetate (A) (700 mg, 2 mmol) together in toluene (10 ml) for 2 h.

2-Acetyl- and 2-Alkoxy carbonylmethylcarbamates (11-22) -- A) General method for preparing carbamates (11-22) by a one-pot reaction-- A typical procedure for

obtaining 2-ethoxycarbonylmethylcarbamate 11 is as follows: A mixture of 2 (120 mg, 0.75 mmol) and phosphonoacetate (A) (261 mg, 0.75 mmol) in toluene (15 ml) was refluxed for 2.5 h under an Ar atmosphere and cooled to room temperature. 18 mg (0.75 mmol) of NaH were added to the reaction mixture, followed by stirring at room temperature for 2 h, washing with brine and drying over MgSO₄. The solvent was evaporated and the residue purified on chromatography by elution with benzene-acetone (30:1) to give 130 mg (76%) of 11 as a colorless oil. B) The synthesis of carbamates (11 and 12) by the Michael addition of carbonyl compounds (8 and 9) -- A solution of 8 (112 mg, 0.49 mmol) in benzene (15 ml) in the presence of NaH (12 mg, 0.5 mmol) was stirred at room temperature for 2 h, washed with brine, dried over MgSO₄ and evaporated. Chromatographic separation of the residue by elution with benzene-acetone (30:1) gave 90 mg (78.3%) of 11 as a colorless oil. By the same method as that above, 12 was obtained in 87.2% yield from 9.

Synthesis of (±)-Hygrine (23) -- A mixture of acetonilcarbamate 17 (333 mg, 1.08 mmol), ethylene glycol (0.8 ml), *p*-toluenesulfonic acid (5 mg) and ethyl orthoformate (1.6 ml) was refluxed for 2.5 h and evaporated under reduced pressure to give an oil, which was dissolved in ether, washed with aq. NaHCO₃ and brine and dried over MgSO₄. Removal of ethylene glycol under reduced pressure gave crude ketal (324 mg), ¹H-nmr (CDCl₃) δ 0.78 (d, *J*=7Hz, 3H, CHCH₃), 0.90 (d, *J*=7Hz, 6H, CH(CH₃)₂), 1.37 (s, 3H, CH₃), 1.00-2.30 (m, 15H, CH₂ x 6, CH x 3), 3.34 (t, *J*=6.7 Hz, 2H, NCH₂), 3.80-4.00 (m, 1H, NCHCH₂), 3.90 (s, 4H, OCH₂CH₂O), 4.40-4.70 (m, 1H, CHOCO). This ketal, which could not be separated into diastereomers, was refluxed for 5 h with LiAlH₄ (61 mg) in abs. THF (2.5 ml). Excess LiAlH₄ was decomposed carefully with H₂O. The reaction mixture was basified with K₂CO₃ and extracted six times with ether. The extract was washed with brine, dried over MgSO₄ and evaporated to give crude aminoketal (287 mg) along with 1-menthol, ¹H-nmr (CDCl₃) δ 1.32 (s, 3H, CCH₃), 2.30 (s, 3H, NCH₃), 3.92 (s, 4H, OCH₂CH₂O). This aminoketal was hydrolyzed with aq. H₂SO₄ (c.H₂SO₄ 90 mg in H₂O 0.4 ml) at room temperature. The reaction mixture was washed with ether to remove 1-menthol, basified with K₂CO₃ and extracted with ether. The extract was washed with brine, dried over MgSO₄ and evaporated carefully to give a crude oil (100 mg) of hygrine 23, which was purified by distillation to give 96 mg (63% overall yield from 17) of 23 as a colorless oil, bp 75°C (18 mmHg), [α]_D=0, ms *m/z* 141 (M⁺), ir (neat) 1710 cm⁻¹, ¹H-nmr (CDCl₃) δ 1.23-2.80 (m, 8H, CH₂ x 4), 2.17 (s, 3H, COCH₃), 2.30 (s, 3H, NCH₃), 3.03 (m, 1H, NCH). Picrate, mp 152-153°C. Anal. Calcd for C₈H₁₅NO·C₆H₃N₃: C, 45.40; H, 4.90; N, 15.13. Found: C, 45.52; H, 4.90; N, 15.18.

2-Oxo-4-(3',4'-dimethoxyphenyl)-1,2,5,6,7,8,9,10-octahydro-trans-quinolizine (25) -- A solution of carbamate 20 (650 mg, 2.7 mmol) in 25% HBr-AcOH (2 ml) was stirred at room temperature overnight and evaporated to give an oil, which was refluxed with saturated HCl-MeOH (1 ml) for 3 h. After evaporation of the solvent, the residue was dissolved in H₂O, basified with K₂CO₃ and extracted five times with EtOAc. The extract was washed with brine, dried over MgSO₄ and evaporated to give crude oil (360 mg) of amine 24, ¹H-nmr (CDCl₃) δ 0.89 (m, 6H, CH₂ x 3), 2.36 (d, *J*=6Hz, 2H, CH₂CO), 2.49-3.19 (m, 4H, NCH₂, NHCH), 3.68 (s, 3H, OCH₃). A

mixture of amine 24 (360 mg), 3,4-dimethoxyacetophenone (531 mg, 2.1 mmol) and CF_3COOH (240 mg, 2.1 mmol) in xylene (50 ml) was refluxed for 48 h and, after dilution with benzene (50 ml), was washed with brine and aq. NaHCO_3 , dried over MgSO_4 and evaporated to give an oil. Chromatographic separation of the latter by elution with CHCl_3 gave 360 mg (22%) of 25 as a yellow oil, exact ms calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_3$ m/z 287.1520 (M^+), obsd m/z 287.1547, ir (CHCl_3) 1720, 1630 cm^{-1} , ^1H -nmr (CDCl_3) δ 0.92-2.82 (m, 8H, $\text{CH}_2 \times 4$), 3.25-3.78 (m, 2H, NCH_2), 3.88 (s, 6H, $\text{OCH}_3 \times 2$), 5.06 (s, 1H, $\text{C}=\text{CHCO}$), 6.81 (s, 1H, aromatic H), 6.88 (s, 2H, aromatic H).

2-Acetylpyperidine (Pelletierine) (26) -- By the same method for obtaining 2-methoxycarbonylmethylpyperidine 24, pelletierine 26 was produced in 86% yield from carbamate 19 as an oil, ms m/z : 141 (M^+), ir (CHCl_3) 3320, 1710 cm^{-1} , ^1H -nmr (CDCl_3) δ 1.10-1.87 (m, 6H, $\text{CH}_2 \times 3$), 2.12 (s, 3H, COCH_3), 2.49 (d, $\underline{J}=5\text{Hz}$, 2H, CHCH_2), 2.40-3.23 (m, 3H, NCH_2 , NCH). Picrate, mp 149-150°C. Anal. Calcd for $\text{C}_8\text{H}_{15}\text{NO} \cdot \text{C}_6\text{H}_3\text{N}_3\text{O}_7$: C, 45.40; H, 4.90; N, 15.13. Found: C, 45.33; H, 4.99; N, 14.86.

rel-(4S,10S)-2-Oxo-4-(3',4'-dimethoxyphenyl)-trans-quinolizidine (27) and rel-(4S,10R)-2-Oxo-4-(3',4'-dimethoxyphenyl)-cis-quinolizidine (29) -- A mixture of pelletierine 26 (154 mg, 1.1 mmol), veratraldehyde (274 mg, 1.65 mmol) and 1% aq. NaOH (2.2 g, 1.6 mmol) was stirred at 70°C for 12 h under an Ar atmosphere, acidified with K_2CO_3 and extracted with CHCl_3 . The extract was washed with brine, dried over MgSO_4 and evaporated to give an oil, which, on chromatographic separation by elution with CHCl_3 -MeOH (40:1), gave 116 mg (44%) of 27 as colorless crystals from the first crop and 50 mg (16%) of 29 as a yellow oil from the second one. 27: mp 78-80°C (lit.¹², mp 83-84°C), ms m/z 289 (M^+), ir (CHCl_3) 2830, 2780, 1710 cm^{-1} , ^1H -nmr (CDCl_3) δ 1.07-2.93 (m, 13H, $\text{CH}_2 \times 6$, CH), 3.21 (dd, $\underline{J}=11\text{Hz}$, 4Hz, 1H, CHAr), 3.87 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.84 (s, 2H, aromatic H), 6.93 (s, 1H, aromatic H). 29: ms m/z , 289 (M^+), ir (CDCl_3) 1710 cm^{-1} , ^1H -nmr (CDCl_3) δ 1.03-3.08 (m, 1H, $\text{CH}_2 \times 6$, CH), 3.88 (s, 6H, OCH_3), 4.21 (dd, $\underline{J}=6\text{Hz}$, 4Hz, 1H, CHAr), 6.72 (s, 2H, aromatic H), 6.78 (s, 1H, aromatic H).

(±)-2-Epilasubine II (28) -- To a solution of 25 (110 mg, 0.38 mmol) in EtOH (2 ml) was added NaBH_4 (40 mg, 1.05 mmol). The reaction mixture was stirred at room temperature for 43 h and evaporated to a semisolid, which was extracted with CHCl_3 . The extract was dried over MgSO_4 and evaporated to give an oily residue, which, on chromatographic separation by elution with CHCl_3 -MeOH (40:1), gave an oil. This oil afforded a colorless powder from hexane. 92 mg (82.5%), mp 137-139°C (lit.¹², mp 141-142°C), exact ms calcd for $\text{C}_{17}\text{H}_{25}\text{NO}_3$ m/z 291.1833 (M^+), obsd m/z 291.1833, ir (CHCl_3) 3600, 3400, 2910, 2840, 2790 cm^{-1} , ^1H -Nmr (CDCl_3) δ 1.07-2.79 (m, 14H, $\text{CH}_2 \times 6$, CH \times 2), 2.89 (dd, $\underline{J}=11\text{Hz}$, 3Hz, 1H, CHAr), 3.64 (br, 1H, OH), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 6.79 (s, 2H, aromatic H), 6.91 (s, 1H, aromatic H). Anal. Calcd for $\text{C}_{17}\text{H}_{25}\text{NO}_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 69.81; H, 8.64; N, 4.46. By the above method, 28 was also obtained from 27 in 65.1% yield and found to be identical in all respect with the 28 above and an authentic sample.

Table II. Physical Properties of the Wittig Reaction Products

- 8 bp 135°C (2 mmHg), ms m/z 229 (M^+), ir (neat) 3350, 1720, 1660 cm^{-1} , 1H -nmr ($CDCl_3$) δ 1.20 (t, $J=7Hz$, 3H, OCH_2CH_3), 1.28 (t, $J=7Hz$, 3H, OCH_2CH_3), 1.52-1.82 (m, 2H, $NHCH_2CH_2$), 2.05-2.38 (m, 2H, $CH_2CH=CH$), 3.15 (q, $J=7Hz$, 2H, $NHCH_2CH_2$), 4.15 (q, $J=7Hz$, 2H, OCH_2CH_3), 4.05 (q, $J=7Hz$, 2H, OCH_2CH_3), 4.77 (br, 1H, NH), 5.79 (dt, $J=16.5Hz$, 1.5Hz, 1H, $CH=CHCO$), 6.90 (dt, $J=16.5Hz$, 6Hz, 1H, $CH=CHCO$).
- 9 bp 120°C (2 mmHg), CI ms m/z 230 ($M^+ + 1$), ir (neat) 3340, 1710, 1650 cm^{-1} , 1H -nmr ($CDCl_3$) δ 1.30 (t, $J=7.5Hz$, 3H, OCH_2CH_3), 1.43-1.80 (m, 4H, $CH_2 \times 2$), 2.03-2.47 (m, 2H, $CH_2CH=CH$), 2.97-3.37 (m, 2H, $NHCH_2$), 3.37 (s, 3H, OCH_3), 4.17 (q, $J=7.5Hz$, 2H, OCH_2CH_3), 4.76 (br, 1H, NH), 5.80 (dt, $J=16.5Hz$, 1Hz, $CH=CHCO$), 6.97 (dt, $J=16.5Hz$, 6Hz, 1H, $CH=CHCO$).
- 10 bp 137°C (2 mmHg), ms m/z 229 (M^+), ir (neat) 3340, 1720 cm^{-1} , 1H -nmr ($CDCl_3$) δ 1.20 (t, $J=7Hz$, 3H, OCH_2CH_3), 1.25 (t, $J=7Hz$, 3H, OCH_2CH_3), 1.52-1.93 (m, 2H, $NHCH_2CH_2$), 2.65 (q, $J=6Hz$, 2H, $CH_2CH=CH$), 3.00-3.43 (m, 2H, $NHCH_2CH_2$), 4.05 (q, $J=7Hz$, 2H, OCH_2CH_3), 4.13 (q, $J=7Hz$, 2H, OCH_2CH_3), 5.17 (br, 1H, NH), 5.77 (d, $J=12Hz$, 1H, $CH=CHCO$), 6.17 (dt, $J=12Hz$, 6.5Hz, 1H, $CH=CHCO$).
- 11 bp 98°C (2 mmHg), ms m/z 229 (M^+), ir (neat) 1730, 1700 cm^{-1} , 1H -nmr ($CDCl_3$) δ 0.58 (t, $J=7Hz$, 6H, $CH_3CH_2 \times 2$), 1.57-2.02 (m, 4H, $CH_2 \times 2$), 2.10-2.50 (m, 2H, CH_2CO), 3.2 (t, $J=6Hz$, CH_2N), 3.97-4.33 (m, 1H, NCH_2), 4.13 (q, $J=7Hz$, 4H, $CH_3CH_2 \times 2$).
- 12 bp 125°C (2 mmHg), ms m/z 229 (M^+), ir (neat) 1730, 1700 cm^{-1} , 1H -nmr ($CDCl_3$) δ 1.23 (t, $J=7.5Hz$, 3H, OCH_2CH_3), 1.39-1.79 (m, 6H, $CH_2CH_2CH_2$), 2.57 (d, $J=7.5Hz$, 2H, CH_2CO), 2.66-3.06 (m, 1H, $HCHN$), 3.68 (s, 3H, OCH_3), 4.10 (q, $J=7.5Hz$, 2H, OCH_2CH_3), 3.79-4.29 (m, 1H, $HCHN$), 4.56-4.89 (m, 1H, NCH_2).
- 14 oil, ms m/z 273 (M^+), ir (neat) 1680, 1610, 1570 cm^{-1} , 1H -nmr ($CDCl_3$) δ 1.43-1.97 (m, 4H, $CH_2 \times 2$), 2.27-2.37 (m, 2H, CH_2CO), 3.20-3.50 (m, 2H, NCH_2), 3.60 (s, 3H, OCH_3), 4.00-4.33 (m, 1H, NCH_2), 6.57 (d, $J=17Hz$, 1H, $COCH=CHPh$), 7.23-7.60 (m, 5H, aromatic H), 7.53 (d, $J=17Hz$, 1H, $COCH=CHPh$).
- 15 bp 121°C (2 mmHg), ms m/z 241 (M^+), ir (neat) 1740, 1700 cm^{-1} , 1H -nmr ($CDCl_3$) δ 1.23 (t, $J=7.5Hz$, 3H, OCH_2CH_3), 1.31-2.11 (m, 4H, $CH_2 \times 2$), 2.11-2.50 (m, 2H, CH_2CO), 3.28-3.54 (m, 2H, NCH_2), 3.95-4.37 (m, 1H, NCH_2), 4.13 (q, $J=7.5Hz$, 2H, OCH_2CH_3), 4.48-4.72 (m, 2H, $CH_2CH=CH_2$), 5.05-5.46 (m, 2H, $CH=CH_2$), 5.72-6.21 (m, 1H, $CH=CH_2$).
- 16 bp 137°C (3 mmHg), ms m/z 325 (M^+), ir (neat) 1740, 1700 cm^{-1} , 1H -nmr ($CDCl_3$) δ 0.78 (d, $J=7Hz$, 3H, $CHCH_3$), 0.90 (d, $J=7Hz$, 6H, $CH(CH_3)_2$), 1.07-2.27 (m, 13H, $CH_2 \times 5$, $CH \times 3$), 2.27-2.53 (m, 2H, CH_2CO), 3.23-3.54 (m, 2H, NCH_2), 3.67 (s, 3H, OCH_3), 4.01-4.38 (m, 1H, NCH_2), 4.38-4.73 (m, $CHOCO$).
- 17 oil, ms m/z 309 (M^+), ir (neat) 1680 cm^{-1} , 1H -nmr ($CDCl_3$) δ 0.78 (d, $J=7Hz$, 3H, $CHCH_3$), 0.90 (d, $J=7Hz$, 6H, $CHMe_2$), 1.08-2.25 (m, 13H, $CH_2 \times 5$, $CH \times 3$), 2.18 (s, 3H, $COCH_3$), 2.25-2.58 (m, 2H, $CHCH_2CO$), 3.22-3.48 (m, 2H, NCH_2), 4.00-4.33 (m, 1H, NCH_2), 4.43-4.73 (m, 1H, $CHOCO$).

(continued)

(continued)

- 18 bp 123-126°C (2 mmHg), ms m/z 199 (M^+), ir (neat) 1690 cm^{-1} , 1H -nmr ($CDCl_3$) δ 1.10-1.77 (m, 6H, $CH_2 \times 3$), 2.17 (s, 3H, $COCH_3$), 2.68 (d, $J=7Hz$, 2H, $CHCH_2CO$), 2.77-3.03 (m, 1H, $HCHN$), 3.65 (s, 3H, OCH_3), 3.80-4.13 (m, 1H, $HCHN$), 4.57-4.87 (m, 1H, CH_2CHN).
- 19 bp 110°C (2 mmHg), CI ms m/z 226 (M^++1), ir (neat) 1750, 1690, 1650 cm^{-1} , 1H -nmr ($CDCl_3$) δ 1.20-1.83 (m, 6H, $CH_2 \times 3$), 2.17 (s, 3H, $COCH_3$), 2.67 (d, $J=8Hz$, CH_2CO), 2.80-3.03 (m, 1H, $HCHN$), 3.87-4.17 (m, 1H, $HCHN$), 4.47-4.63 (m, 2H, $CH_2CH=CH_2$), 4.63-4.93 (m, 1H, $NCHCH_2$), 5.07-5.43 (m, 2H, $CH_2CH=CH_2$) 5.70-6.17 (m, 1H, $CH_2CH=CH_2$).
- 20 bp 110°C (2 mmHg), ms m/z 241 (M^+), ir (neat) 1750, 1690, 1650 cm^{-1} , 1H -nmr ($CDCl_3$) δ 1.20-1.87 (m, 6H, $CH_2 \times 3$), 2.58 (d, $J=7Hz$, 2H, $CHCH_2CO$), 2.67-3.07 (m, 1H, $HCHN$), 3.63 (s, 3H, OCH_3), 3.90-4.20 (m, 1H, $HCHN$), 4.50-4.65 (m, 2H, $OCH_2CH=$), 4.65-4.90 (m, 1H, $NCHCH_2$), 5.08-5.45 (m, 2H, $CH_2CH=CH_2$), 5.72-6.18 (m, 1H, $CH_2CH=CH_2$).
- 21 bp 124°C (0.2 mmHg), ms m/z 323 (M_+), ir (neat) 1690 cm^{-1} , 1H -nmr ($CDCl_3$) δ 0.77 (d, $J=7Hz$, 3H, $CHCH_3$), 0.88 (d, $J=7Hz$, 6H, $CH(CH_3)_2$), 1.35-2.45 (m, 15H, $CH_2 \times 6$, $CH \times 3$), 2.17 (s, 3H, $COCH_3$), 2.65 (d, $J=7.5Hz$, 2H, CH_2CO), 2.75-3.28 (m, 1H, $HCHN$), 3.85-4.25 (m, 1H, $HCHN$), 4.38-4.91 (m, 2H, $NCHCH_2$, $CHOCO$).
- 22 mp 85-86°C, ms m/z 287 (M^+), ir (neat) 1690 cm^{-1} , 1H -nmr ($CDCl_3$) δ 1.33-1.90 (m, 6H, $CH_2 \times 3$), 2.70-3.13 (m, 1H, $HCHN$), 2.92 (d, $J=7Hz$, 2H, CH_2CO), 3.68 (s, 3H, OCH_3), 3.83-4.25 (m, 1H, $HCHN$), 4.67-5.00 (m, 1H, $NCHCH_2$), 6.75 (d, $J=16Hz$, $COCH=CHPh$), 7.33-8.63 (m, 5H, aromatic H), 8.02 (d, $J=16Hz$, $COCH=CHPh$).

Table III. Results of Elemental Analyses of the Wittig Reaction Products*

Compound	Molecular Formula	Calculated			Found		
		C	H	N	C	H	N
<u>8</u>	$C_{11}H_{19}NO_4$	57.62	8.35	6.11	57.34	8.52	6.16
<u>9</u>	$C_{11}H_{19}NO_4$	57.62	8.35	6.11	57.76	8.58	6.21
<u>10</u>	$C_{11}H_{19}NO_4$	57.62	8.35	6.11	57.88	8.45	6.08
<u>11</u>	$C_{11}H_{19}NO_4$	57.62	8.35	6.11	57.84	8.49	6.12
<u>12</u>	$C_{11}H_{19}NO_4$	57.62	8.35	6.11	57.48	8.46	6.29
<u>13</u>	$C_{10}H_{17}NO_3$	60.28	8.60	7.03	60.03	8.79	7.04
<u>15</u>	$C_{12}H_{19}NO_4$	59.73	7.94	5.81	59.20	7.97	5.70
<u>16</u>	$C_{18}H_{13}NO_4$	66.43	9.60	4.30	66.43	9.85	4.37
<u>18</u>	$C_{10}H_{17}NO_3$	60.28	8.60	7.30	60.24	8.76	7.02
<u>19</u>	$C_{11}H_{19}NO_3$	63.97	8.50	6.22	63.11	8.47	6.39
<u>20</u>	$C_{12}H_{19}NO_4$	59.73	7.94	5.81	59.45	7.77	5.84
<u>21</u>	$C_{19}H_{33}NO_3$	70.55	10.41	4.33	69.70	10.41	4.30

* 14: Exact mass calcd for $C_{16}H_{19}NO_3$ m/z 273.1363 (M^+), obsd m/z 273.1357.22: Exact mass calcd for $C_{17}H_{21}NO_3$ m/z 287.1519 (M^+), obsd m/z 287.1501

ACKNOWLEDGMENT

Professor C. Kibayashi (Tokyo College of Pharmacy) is gratefully acknowledged for providing the ir and ¹H-nmr spectral data of 2-epilasubine II.

REFERENCES AND NOTES

1. Examples: Y. Nagao, W-M. Dai, M. Ochiai, S. Tsukagoshi, and E. Fujita, J. Am. Chem. Soc., 1988, 110, 289; D. L. Comins, M. A. Weglarz, and S. O'Connor, Tetrahedron Lett., 1988, 29, 1751; S. Arseniyadis, P. Q. Huang, and H. P. Husson, Tetrahedron Lett., 1988, 29, 1391.
2. T. Nagasaka, H. Tamano, T. Maekawa, and F. Hamaguchi, Heterocycles, 1987, 26, 617.
3. T. Nagasaka, H. Tamano, and F. Hamaguchi, Heterocycles, 1986, 24, 1231.
4. a) For Wittig reactions of α -hydroxycarbamates to give ω -amino- α,β -unsaturated esters: T. Shono, Y. Matsumura, T. Kanazawa, M. Habuka, K. Uchida, and K. Toyoda, J. Chem. Research (S), 1984, 320. b) For Wittig reactions of α -hydroxycarbamates followed by intramolecular Michael addition of products: K. Shishido, Y. Sukegawa, K. Fukumoto, and T. Kametani, J. Chem. Soc., Perkin Trans I, 1987, 993. c) For Wittig reactions using ω -hydroxylactams: J. J. de Boer and W. N. Speckamp, Tetrahedron Lett., 1975, 4039 and reference 9a.
5. The 2-isomer of 9 could not be detected.
6. The reaction of 2 with a Wittig reagent in the presence of sodium hydride in refluxing toluene failed to give the desired amine 11. For discussion about this reaction condition, see reference 4b.
7. The piperidine hydroxycarbamates (5-7) could be easily converted to the corresponding enamines and sometimes gave dimers. See reference 11.
8. L. A. Carpino, J. Chem. Soc. Chem. Comm. 1966, 859.
9. a) T. Wakabayashi and M. Saito, Tetrahedron Lett., 1977, 93. b) K. Th. Wanner and A. Kartner, Heterocycles, 1987, 26, 921.
10. T. Shono, H. Hamaguchi, and Y. Matsumura, J. Am. Chem. Soc., 1975, 97, 4264.
11. T. Nagasaka, H. Hayashi, and F. Hamaguchi, Heterocycles, 1988, 27, 1685.
12. H. Iida, M. Tanaka, and C. Kibayashi, J. Org. Chem., 1984, 49, 1909.
13. The ratio of these types of trans- and cis-quinolizidine derivatives has been found to vary by the reaction conditions: J. Quick and R. Oterson, Tetrahedron Lett., 1977, 603.

Received, 1st August, 1988