SYNTHESIS OF (±)-ROXBURGHILIN AND (±)-EPIROXBURGHILIN[1]

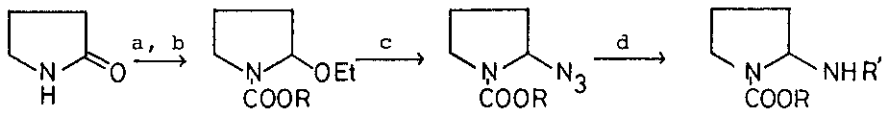
Tatsuo Nagasaka,* Hiroto Yamamoto, Akio Sugiyama, and
Fumiko Hamaguchi
Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji,
Tokyo 192-03, Japan

Abstract — The synthesis of (±)-roxburghilin (15) and (±)-epiroxburghilin (16) in six steps from 2-pyrrolidinone is described.

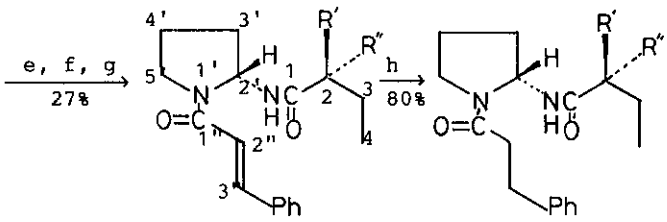
The preceding paper[2] reported the reaction by which O-, S-, N- and C-functional groups are introduced at the α-position of N-alkoxycarbonylpyrrolidines, starting from 2-pyrrolidinone. The present paper describes the application of this method to the alkaloid synthesis of (±)-roxburghilin and (±)-epiroxburghilin[1] [(±)-odorine and (±)-epiodorine][3]. (+)-Roxburghilin [(+)-odorine], an alkaloid consisting of a bis-amide of 2-aminopyrrolidine, comes from the leaves of Aglaia roxburgiana[1] and Aglaia odorata[3] (Meliaceae), the latter a medicinal plant in Thailand.[3]

2-Azidourethanes (4 and 5)[2] were obtained from the corresponding 2-ethoxyurethanes (2 and 3)[4] in high yields. Their catalytic hydrogenation over 5% palladium-carbon afforded labile amines 8 and 12. Amine 8, without purification, was acetylated with acetic anhydride to amide 9 in 21% yield and condensed with (±)-2-methylbutyric acid by diphenyl phosphorazidate (DPPA) to give amide 10 in 12.4% yield in a diastereomeric mixture. Reaction of 8 (crude) with the mixed anhydride (6), prepared in situ by the condensation of (±)-2-methylbutyric acid with ethyl chloroformate in the presence of triethylamine, afforded amide 10 in 19% yield, along with the bis-carbamate (11) in 2.2% yield. The lower yields of amides 9 and 10 appeared to due to the instability of amine 8. Removal of the ethoxycarbonyl group at the N-position from amide 10 under various basic conditions was

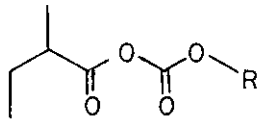
Scheme



1 2: R=Et (83%) 3: R=Bu^t (88%) 4: R=Et (99%) 5: R=Bu^t (90%) 8: R=Et, R'=H 9: R=Et, R'=Ac (21%) 10: R=Et, R'=COCH(Me)Et (19%) 11: R=Et, R'=COOEt (2.2%) 12: R=Bu^t, R'=H 13: R=Bu^t, R'=COCH(Me)Et (43%) 14: R-Bu^t, R'=COOBu^i (28%)



15: R'=H, R"=Me 16: R'=Me, R"=H 17: R'=H, R"=Me 18: R'=Me, R"=H



a: 1) NaH/C_6H_6 2) EtOOCCl or $(Boc)_2O$ 6: R=Et

b: $NaBH_4$/EtOH-H^+ c: TMS-N_3/$ZnCl_2$-CH_2Cl_2 7: R=Bu^i

d: 5%Pd-C/EtOH/6 or 7/H_2 (2 atm) e: 1) Me_3SiI 2) MeOH f: PhCH=CHCOCl/Py

g: preparative tlc (C_6H_6:CH_2Cl_2:i-PrOH=48:48:4) h: 5%Pd-C/EtOAc/H_2 (2 atm)

attempted but without success. Catalytic hydrogenation of the azide (5) over 5% palladium-carbon in the presence of a pure mixed-anhydride (7) and triethylamine increased the yield of the desired product (13) to 43%, but the bis-carbamate (14) was also obtained as a by-product in 28% yield. Removal of the tert-butoxycarbonyl group at the N-position from 13 proceeded smoothly by reaction of this compound with trimethylsilyl iodide[5] followed by methanolysis to give the amine, which was, without purification, converted by reaction with trans-cinnamoyl chloride in pyridine to a mixture of (±)-roxburghilin (15) and (±)-epiroxburghilin (16) in 27% yield. These diastereomers (15 and 16) were separated by a method described in the literature.[6] The spectroscopic properties of the synthetic products (15 and 16) were identical with those of the natural products as stated by Connolly et al.[1] The hydrogenation of a mixture of roxburghilin (15) and epiroxburghilin (16) afforded an inseparable mixture of dihydroroxburghilin (17) and epidihydroroxburghilin (18).[1]

EXPERIMENTAL

All melting points were determined by micro-melting point apparatus (Yanagimoto) without correction. Ir and mass specta were measured on a Hitachi 200-10 and Hitachi M-80 spectrometer, respectively. ^{1}H-Nmr spectra were recorded on a Varian EM-390 and/or a Brucker AM-400 spectrometer. 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 syntheses of compounds 2, 3, 4, and 8 are reported in our preceeding papers (references 2 and 4).

2-Azido-1-tert-butoxycarbonylpyrrolidine (5) -- Me_3SiN_3 (173 mg, 1.5 mmol) and $ZnCl_2$ (5 mg, 0.04 mmol) were added to a solution of 3 (215 mg, 1 mmol) in CH_2Cl_2 (10 ml) under an Ar atmosphere. The reaction mixture was stirred at room temperature for 12 h, washed with H_2O, dried over $MgSO_4$ and evaporated to give a yellow oil which, on chromatographic separation by elution with benzene, gave 200 mg (90%) of 5 as a colorless oil. Ir (neat) cm^{-1} ν: 2100, 1700. Ms m/z: 170 (M^+-N_3). ^{1}H-Nmr ($CDCl_3$) δ:1.50 (s, 9H, Bu), 1.70-1.21 (m, 4H, CH_2 x 2), 3.20-3.60 (m, 2H, NCH_2), 5.47 (m, 1H, $NCHN_3$). Anal. Calcd for $C_9H_{16}N_4O_2$: C, 50.93; H, 7.60; N, 26.40. Found: C, 51.04; H, 7.84; N, 26.09.
Mixed Anhydride (7) -- To a mixture of (±)-2-methylbutyric acid (4.08 g, 40 mmol) and iso-butyl chloroformate (5.48 g, 40 mmol) in toluene (50 ml) was added Et_3N (4.04 g, 40 mmol). After stirring at room temperature for 30 min, the reaction mixture was diluted with benzene (100 ml), washed with H_2O, 5% $NaHCO_3$, 5% HCl and brine, dried over $MgSO_4$ and evaporated to give an oil which, on distillation, gave 6.67 g (82.5%) of 7 as a colorless oil, bp 45-50 °C (2 mmHg). ^{1}H-Nmr ($CDCl_3$) δ: 0.96 [d, J=8Hz, 6H, $CH(CH_3)_2$], 0.96 (t, J=8Hz, 3H, CH_2CH_3), 1.21 (d, J=8Hz, 3H, $CHCH_3$), 1.35-2.22 (m, 3H, CH_2, CH), 2.28-2.67 (m, 1H, COCH), 4.03 (d, J=8 Hz, 2H, OCH_2).
2-Acetylamino-1-ethoxycarbonylpyrrolidine (9) -- A mixture of 4 (100 mg) and 5% Pd-C (20 mg) in Et_2O (20 ml) was subjected to catalytic hydrogenation at room temperature for 12 h under 2 atm of hydrogen pressure. The catalyst was removed by filtration and the filtrate was concentrated to an oil which was subsequently allowed to stand for one day with Ac_2O (1 ml). Evaporation of the excess Ac_2O gave a yellow oil which, on chromatographic separation by elution with $CHCl_3$, gave 23 mg (21%) of 9 as a colorless oil. Ir (neat) cm^{-1} ν: 3280, 1700, 1660. Ms m/z: 200 (M^+). ^{1}H-Nmr ($CDCl_3$) δ: 1.29 (t, J=7Hz, 3H, CH_2CH_3), 1.93 (s, 3H, $COCH_3$), 1.62-2.25 (m, 4H, CH_2 x 2), 3.08-3.68 (m, 2H, CH_2N), 4.13 (q, J=7Hz, 2H, OCH_2CH_3), 5.65 (br, 1H, NCHN), 6.10 (br, 1H, CONH).
1-Ethoxycarbonyl-2-(2-methylbutyryl)aminopyrrolidine (10) -- a) To a solution of crude 8 (765 mg, 4.8 mmol) and (±)-2-methylbutyric acid (612 mg, 6 mmol) in DMF (3 ml) was added at 0°C a solution of diphenyl phosphorazidate (DPPA) (1.65 g, 6

mmol) in DMF (2 ml) followed by the addition of Et_3N (707 mg, 7 mmol). The reaction mixture was stirred at 0°C for 1 h and then at room temperature for 20 h. EtOAc and H_2O were added to the DMF solution. The aqueous layer separated was extracted with EtOAc three times. The combined organic layers were washed with 5% HCl, 5% $NaHCO_3$ solution and brine and dried over $MgSO_4$. Evaporation of the solvent gave an oil which, on chromatographic separation by elution with benzene-acetone (10 : 1), gave 145 mg (12.4%) of 10 as a solid. Recrystallization from isopropyl ether afforded pure 10 as colorless prisms, mp 84-85°C. Ir (KBr) cm^{-1} ν: 3300, 1700, 1640. Ms m/z: 242 (M^+). ^{1}H-Nmr ($CDCl_3$) δ: 0.88 (t, J=7.5Hz, 3H, CH_2CH_3), 1.12 (d, J=7.5Hz, 3H, $CHCH_3$), 1.23 (t, J=7.5Hz, 3H, OCH_2CH_3), 1.7-2.2 (m, 7H, CH_2CH_3, $CHCH_3$, CH_2 x 2), 3.20-3.70 (m, 2H, NCH_2), 4.13 (q, J=7.5Hz, 2H, OCH_2CH_3), 5.46-5.77 (m, 2H, NCH, NH). Anal. Calcd for $C_{12}H_{22}N_2O_3$: C, 59.48; H, 9.15; N, 11.56. Found: C, 59.40; H, 9.37; N, 11.57. Compound 10 appeared to be a mixture of diastereomers, judging from the fine signals of its ^{1}H-nmr spectrum, which could not be distinguished from each other by tlc. b) Et_3N (467 mg, 4.6 mmol) was added to an ice-cooled solution of (±)-2-methylbutyric acid (471 mg, 4.6 mmol) and ethyl chloroformate (501 mg, 4.6 mmol) in toluene (6 ml). The reaction mixture was stirred at 0°C for 15 min and then at room temperature for 15 min. A solution of crude 8 (730 mg, 4.6 mmol) in toluene (1 ml) was added to this solution of mixed anhydride (6) under ice-cooling and stirred at 0°C for 50 min and then at room temperature for 50 min. EtOAc (100 ml) was added to this reaction mixture and the EtOAc extract was washed with H_2O, 5% $NaHCO_3$ solution and brine and dried over $MgSO_4$ and evaporated. The residue, on chromatographic separation by elution with benzene-acetone (10 : 1), gave 23 mg (2.2%) of bis-urethane (11) as a colorless oil from the first crop, bp 98-100°C (5 mmHg). Ir (neat) cm^{-1} ν: 3300, 1730, 1670. Ms m/z: 229 (M^+-1). ^{1}H-Nmr ($CDCl_3$) δ: 1.25 (q, J=7.5Hz, 6H, OCH_2CH_3 x 2), 1.70-2.17 (m, 4H, CH_2 x 2), 3.13-3.67 (m, 2H, NCH_2), 4.12 (q, J=7.5Hz, 2H, OCH_2CH_3), 4.14 (q, J=7.5Hz, 2H, OCH_2CH_3), 5.10 (br. 1H, NH), 5.45 (m, 1H, NCHNH). Anal. Calcd for $C_{10}H_{18}N_2O_4$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.36; H, 8.12; N, 11.89. From the second crop, 212 mg (19%) of 10 were obtained as colorless prisms.

1-tert-Butoxycarbonyl-2-(2-methylbutyryl)aminopyrrolidine (13) -- A mixture of 5 (4.0 g, 18.9 mmol), 7 (3.82 g, 18.9 mmol), and 5% Pd-C (1 g) in EtOH (50 ml) was subjected to catalytic hydrogenation at room temperature for 5 h under 2 atm of hydrogen pressure. The catalyst was removed by filtration and the filtrate was concentrated to give a crystalline solid which, on chromatographic separation by elution with benzene-acetone (10 : 1), gave 1.5 g (28%) of bis-carbamate (14) from the first crop and 2.2 g (43%) of 13 from the second crop. 13: Colorless prisms from isopropyl ether, mp 144-147°C. Ir (KBr) cm^{-1} ν: 3250, 1700, 1640, 1550. Ms m/z: 270 (M^+). ^{1}H-Nmr ($CDCl_3$) δ: 0.88 (t, J=7.5Hz, 3H, CH_2CH_3), 1.12 (d, J=7.5Hz, 3H, $CHCH_3$), 1.43 (s, 9H, OBu), 1.70-2.23 (m, 7H, CH_2CH_3, $CHCH_3$, CH_2 x 2), 3.07-3.60 (m, 2H, NCH_2), 5.40-5.93 (m, 2H, NCHNH). Anal. Calcd for $C_{14}H_{26}N_2O_3$: C, 62.19; H, 9.69; N, 10.36. Found: C, 62.36; H, 9.70; N, 10.23. Compound 13 appeared to be a mixture of diastereomers from its ^{1}H-nmr spectrum; they could not be distinguished from each other by tlc. 14: Colorless prisms from isopropyl ether, mp 92-95°C. Ir (KBr) cm^{-1} ν: 3300, 1760, 1680. Ms (CI) m/z: 287 (M^++1). ^{1}H-Nmr ($CDCl_3$) δ: 0.90 [d, J=7.5Hz, 6H, $CH(CH_3)_2$], 1.43 (s, 9H, Bu), 1.6-2.1 [m,

5H, C<u>H</u>$(CH_3)_2$, CH_2 x 2], 3.13-3.6 (m, 2H, NCH_2), 3.82 (d, <u>J</u>=7.5Hz, 2H, OCH_2CH), 4.90 (br. 1H, NH), 5.3-5.53 (m, 1H, NCHN). <u>Anal</u>. Calcd for $C_{14}H_{26}N_2O_4$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.39; H, 9.18; N, 9.65.

<u>(±)-Roxburghilin (15) and (±)-Epiroxburghilin (16)</u> -- Me_3SiI (0.17 ml, 1.2 mmol) was added to a solution of <u>13</u> (270 mg, 1 mmol) in $CHCl_3$ (5 ml) under an Ar atmosphere. The reaction mixture was stirred at room temperature for 30 min and evaporated after adding MeOH (120 mg, 3.8 mmol) to give an oil which was mixed with <u>trans</u>-cinnamoyl chlolide (200 mg, 1.2 mmol) and pyridine (10 ml) and stirrerd at room temperature for one day. The reaction mixture was extracted with EtOAc and the extract was washed with 5% HCl, 5% $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated. The residue was chromatographed by elution with benzene-acetone (20 : 1) to give 81 mg (27%) of a mixture of <u>15</u> and <u>16</u>. Recrystallization of this mixture from benzene gave colorless needles, mp 174-176°C. The preparative tlc (high performance tlc, Merck) of this mixture by elution with benzene-dichloromethane-isopropanol (48:48:4)[6] was repeated ten times to give pure <u>15</u> as a polar product and pure <u>16</u> as a less polor product (ratio 1:1). <u>15</u>: Colorless needles from benzene, mp 187-190°C. Ir (KBr) cm^{-1} ν: 3430, 1670, 1642, 1600. Ms m/z: 300 (M^+). ^{1}H-Nmr (400MHz) ($CDCl_3$) δ: 0.78 (t, <u>J</u>=7.4Hz, 3H, 4-CH_3), 1.14 (d, <u>J</u>=6.9Hz, 3H, 2-CH_3), 1.39 (m, 1H, 3-C<u>H</u>H), 1.63 (m, 1H, 3-CH<u>H</u>), 1.84-2.02 (m, 3H, 4'-CH_2, 2-CH), 2.09 (m, 1H, 3'-C<u>H</u>H), 2.23 (m, 1H, 3'-CH<u>H</u>), 3.49 (m, 1H, 5'-C<u>H</u>H), 3.74 (m, 1H, 5'-CH<u>H</u>), 6.10 (m, 1H, 2'-CH), 6.15 (m, 1H, NH), 6.96 (d, <u>J</u>=15.4Hz, 2"-CH), 7.26-7.38 (m, 3H, aromatic H x 3), 7.53-7.57 (m, 2H, aromatic H x 2), 7.69 (d, <u>J</u>=15.4Hz, 3"-CH). <u>Anal</u>. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 72.03; H, 7.95; N, 9.21. <u>16</u>: Colorless needles from benzene, mp 174-177°C. Ir (KBr) cm^{-1} ν: 3440, 1670, 1640, 1600. Ms m/z: 300 (M^+). ^{1}H-Nmr (400MHz) ($CDCl_3$) δ: 0.90 (t, <u>J</u>=7.4Hz, 3H, 4-CH_3), 1.06 (d, <u>J</u>=6.8Hz, 3H, 2-CH_3), 1.44 (m, 1H, 3-C<u>H</u>H), 1.69 (m, 1H, 3-CH<u>H</u>), 1.80-2.00(m, 3H, 4'-CH_2, 2-CH), 2.10 (m, 1H, 3'-C<u>H</u>H), 2.15 (m, 1H, 3'-CH<u>H</u>), 3.48 (m, 1H, 5'-C<u>H</u>H), 3.72 (m, 1H, 5'-C<u>H</u>H), 6.15 (m, 1H, 2'-CH), 6.20 (br, 1H, NH), 6.93 (d, <u>J</u>=15,4Hz, 1H, 2"-CH), 7.35 (m, 3H, aromatic H x 3), 7.54 (m, 2H, aromatic H x 2), 7.68 (d, <u>J</u>=15.4Hz, 1H, 3"-CH). <u>Anal</u>. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 72.22; H, 7.97; N, 9.17.

<u>Mixture of Dihydroroxburghilin (17) and Epidihydroroxburghilin (18)</u> -- A mixture (50 mg) of <u>15</u> and <u>16</u> in EtOAc (5 ml) was hydrogenated over 5% Pd-C (25 mg) for 15 min under 2 atm of hydrogen pressure. The catalyst was filtered off and the solvent was evaporated to give a crystalline solid which, on recrystallization from $CHCl_3$-petroleum ether, gave 41 mg (80%) of a mixture of <u>17</u> and <u>18</u> as colorless needles. This mixture showed one spot on tlc under various conditions and could not be completely separated though several attempts were made to do so. mp 112-114°C. Ms m/z: 302 (M^+). ^{1}H-Nmr ($CDCl_3$) δ: 0.92 (t, <u>J</u>=7.5Hz, 3H, $CH_2C\underline{H}_3$), 1.13 (d, <u>J</u>=8Hz, 3H, $CHC\underline{H}_3$), 1.27-2.46 (m, 7H, $C\underline{H}_2CH_3$, $C\underline{H}CH_3$, CH_2 x 2), 2.46-2,93 (m, 2H, $COCH_2$), 2.93-3.23 (m, 2H, $PhCH_2$), 3.23-3.87 (m, 2H, NCH_2), 5.43-6.20 (m, 1H, NC<u>H</u>NH), 6.20-6.53 (m, 1H, NH), 7.40 (1br, 5H, aromatic H). <u>Anal</u>. Calcd for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.71; H, 8.65; N, 9.25.

ACKNOWLEDGMENT

We wish to thank professor Connolly (University of Glasgow) for providing the ^{1}H- and ^{13}C-nmr spectra of roxburghilin and epiroxburghilin.

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Received, 20th May, 1988