A SYNTHESIS OF PANDACA ALKALOIDS, 20αH-DIHYDROCLEAVAMINE AND 20βH-DIHYDROCLEAVAMINE#

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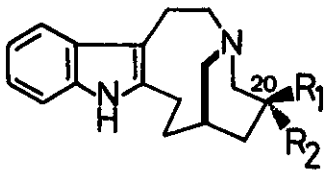
Abstract-----Alkaloids of Pandaca eusepala, 20αH-dihydrocleavamine and 20βH-dihydrocleavamine, have been synthesized in dl form using a α-diketone monothioketal intermediate.

Cleavamine type alkaloids had been only known as degradation products of the oncolytic double alkaloids[1], vinblastine and vincristine, and the iboga alkaloid, catharanthine[2], before 20αH-dihydrocleavamine(1) and 20βH-dihydrocleavamine(2) were isolated from the Apocyanaceae plant, Pandaca eusepala, by a French group[3]. We report here a new synthesis[4] of these alkaloids, (1) and (2), using the cleavage reaction of a α-diketone monothioketal intermediate[5].

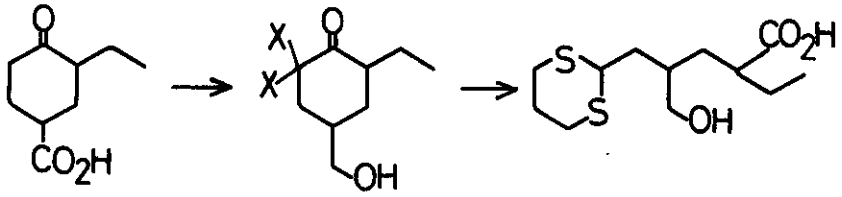
Ethylene ketalization of the known keto-acid[6](3), followed by reduction with lithium aluminum hydride and acid hydrolysis gave the keto-alcohol(4) in 70.5 % overall yield. Reaction of a hydroxymethylene ketone derivative of (4) with trimethylene dithiotosylate[7,8] furnished the α-diketone monothioketal(5) in 29 % overall yield. Cleavage of (5) using potassium hydroxide in warm tert butyl alcohol[9] underwent smooth cleavage to give the carboxylic acid(6) which on reflux in benzene in the presence of p-toluenesulfonic acid afforded the δ-lactone(7) in 66 % overall yield. Condensation of (7) with tryptamine at 160 °C gave the amide(8) in 90 % yield. In these conversions all the reactions were carried out using a mixture of epimers and no separation of each epimer was attempted.

This article is dedicated to Professor Tetsuji Kametani on the occasion of his retirement from Pharmaceutical Institute, Tohoku University.



(1) R_1=Et, R_2=H

(2) R_1=H, R_2=Et

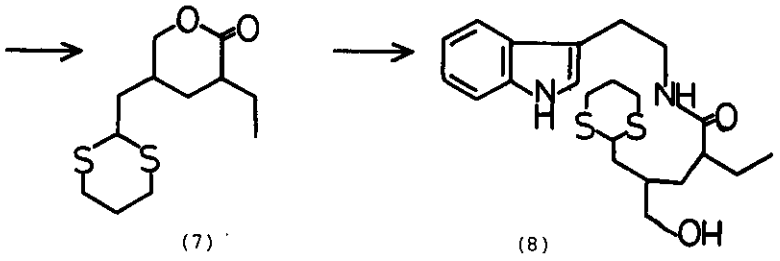


(3)

(4) X=H_2

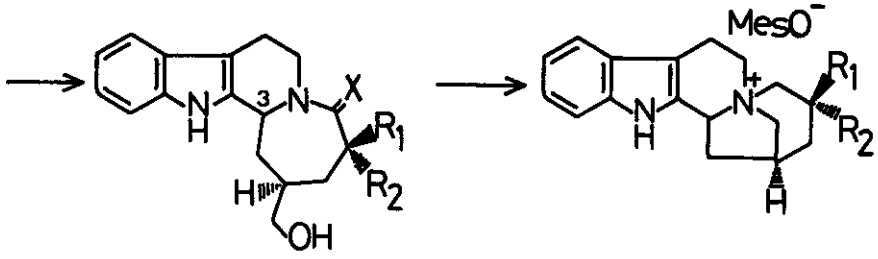
(5) X=-S$(CH_2)_3$S-

(6)



(7)

(8)



(9) a; R_1=Et, R_2=H, X=O

b; R_1=H, R_2=Et, X=O

(10) a; R_1=Et, R_2=H, X=H_2

b; R_1=H, R_2=Et, X=H_2

(11) a; R_1=Et, R_2=H

b; R_1=H, R_2=Et

On hydrolysis of the dithiane group[10], by treatment of (8) with methyl iodide in aqueous acetonitrile at room temperature, concomitant cyclization[11] occurred to give two products, αH-lactam(9a) and βH-lactam(9b), in yields of 39 % and 18 % after a silica gel column chromatography. On a silica gel tlc plate there could be recognized two other cyclization producs(Ehrlich test negative), however their amounts were too small to be isolated. At this stage, we were not interested in the stereochemistry of C-3 center of the cyclization products, since the chirality of C-3 center has to be disappeared at the later stage of the synthesis. Reduction of (9a) with lithium aluminum hydride in boiling tetrahydrofuran gave the corresponding amino-alcohol(10a) in 83 % yield. Treatment of (10a) with methanesulfonyl chloride in the presence of triethylamine, followed by refluxing the crude mesylate in chloroform gave the pentacyclic quaternary mesylate(11a), which on dissolving metal reduction[4a] furnished (±)-20αH-dihydrocleavemine(1) in 30 % overall yield from (10a). Similarly-the βH-lactam(9b) was reduced to the corresponding amino-alcohol(10b) in 57 % yield and the following conversion allowed a formation of (±)-20βH-dihydrocleavamine(2) in 30 % overall yield from (10b). Structure of (2) was determined by a comparison with the authentic specimen prepared by a different route[4b].

EXPERIMENTAL SECTION

2-Ethyl-4-hydroxymethylcyclohexanone(4) A mixture of (3)[6](88.0 g, 518 mmol), and ethyleneglycol(33.9 g, 546 mmol) in benzene(300 ml) was refluxed in the presence of a catalytic amount of p-toluenesulfonic acid using a Dean-Stark head until no more water was collected(3.5 h). The reaction mixture was washed with water and saturated NaCl, and dried over Na_2SO_4. Removal of the solvent in vacuo gave the crude ethyleneketal carboxylic acid(115.0 g) as a colorless oil. To an ice-cooled solution of lithium aluminum hydride(25.0 g, 659 mmol) in ether(700 ml) under N_2 was added dropwise a solution of the crude ethyleneketal carboxylic acid(115.0 g) in ether(200 ml) over a period of 2.5 h. After stirring at room temperature for 10 h, the reaction mixture was cooled in an ice bath and treated carefully with aqueous ether. The resulting sludge was filtered through Celite and the filtrate was washed with saturated NaCl and dried over Na_2SO_4. Removal of the solvent in vacuo gave the alcohol as a colorless oil(80.0 g), which was hydrolyzed with 1N H_2SO_4(250 ml) in refluxing ethanol(250 ml) for 3 h. Most of ethanol was removed in vacuo and the residue was extracted with ether. The extract was washed with water and saturated NaCl, and dried over Na_2SO_4. Removal of the solvent in vacuo afforded a yellow oil

which, upon distillation in vacuo, gave (4)(total yield 57.0 g, 70.5 %) as a colorless oil: bp 90∿91 °C(0.25 mm); IR(neat) 3350, 1700 cm^{-1}; NMR($CDCl_3$) δ 0.87(3H, t, J=7.0 Hz), 1.00∿2.50(10H, m), 3.30(1H, s, disapp. with D_2O), 3.60(2H, m); MS m/e 156(M^+), 55(100 %).

Anal. ($C_9H_{16}O_2$) C, H.

α-Diketone monothioketal(5) To a stirred solution of sodium ethoxide, prepared by dissolving sodium metal(25.3 g, 1.1 g-atm) in ethanol(500 ml), with cooling in an ice bath under N_2 was added a mixture of (4)(57.4 g, 368 mmol) and ethyl formate(81.8 g, 1.1 mole) in ethanol(100 ml). After stirring at room temperature for 24 h, most of ethanol was removed in vacuo and the residue was extracted with water. The aqueous layer was washed with benzene, and extracted methylene chloride after acidification with concd.HCl. The extract was washed with water and saturated NaCl, and dried over Na_2SO_4. Removal of the solvent in vacuo gave the hydroxymethylene ketone(57.2 g) as a pale red oil, which was used without further purification.

A mixture of the crude hydroxymethylene ketone(57.2 g), trimethylene dithiotosylate[7](112.3 g, 270 mmol) and freshly fused potassium acetate(91.2 g, 930 mmol) in ethanol(560 ml) was refluxed under N_2 for 4.5 h. Most of ethanol was removed in vacuo and the residue was extracted with ether. The extract was washed with water, 2N NaOH, and saturated NaCl and dried over Na_2SO_4. Removal of the solvent in vacuo afforded a dark red oil(89.7 g), which was purified by column chromatography on silica gel. Elution with chloroform gave (5)(total yield 28.1 g, 29.4 %) as a pale yellow oil: IR(neat) 3370, 1700 cm^{-1}; NMR($CDCl_3$) δ 0.93(3H, t, J=7.0 Hz), 1.10∿2.95(12H, m), 3.00(1H, s, disapp. with D_2O), 3.05∿4.00(4H, m); MS m/e 260(M^+), 201(100 %).

Anal. ($C_{12}H_{20}O_2S_2$) C, H, S.

2-Ethyl-4-[2,2-(propane-1,3-dithio)ethyl]-δ-valerolactone(7) A mixture of (5)(2.60 g, 10.0 mmol) and ground KOH(2.10 g, purity 80 %, 30.0 mmol) in tert butyl alcohol(30 ml) was refluxed for 3 h. Most of tert butyl alcohol was removed in vacuo and residue was extracted with water. The aqueous layer was washed with ether, and extracted with ether after acidification with concd.HCl. The extract was washed with saturated NaCl and dried over Na_2SO_4. Removal of the solvent in vacuo afforded the carboxylic acid(6)(2.50 g) as a pale yellow viscous oil.

A mixture of the crude(6)(2.50 g) was refluxed in benzene in the presence of a catalytic amount of p-toluenesulfonic acid using a Dean-Stark head until no more water was collected(45 min). Removal of the solvent in vacuo afforded a pale yellow

viscous oil(2.45 g) which was purified by column chromatography on silica gel. Elution with methylene chloride afforded pale yellow crystals, which were recrystallized from ethanol to give (7)(1.72 g, 66.2 % from 5) as colorless crystals: mp 80∿81 °C; IR(Nujol) 1730, 1160 cm^{-1}; NMR($CDCl_3$) δ 1.00(3H, t, J=7.0 Hz), 1.60∿3.10(14H, m), 3.83∿4.50(3H, m); MS m/e 260(M^+), 119(100 %).

Anal. ($C_{12}H_{20}O_2S_2$) C, H, S.

N-[2-(3-Indolyl)ethyl]-3-ethyl-4-hydroxymethyl-6,6-(propane-1,3-dithio)hexamide (8) A mixture of (7)(530 mg, 2.00 mmol) and tryptamine(384 mg, 2.40 mmol) was heated under N_2 at 160 °C for 30 min. The reaction mixture was dissolved in chloroform and the solution was washed with 6 % HCl and saturated NaCl, and dried over Na_2SO_4. Removal of the solvent in vacuo afforded a brown viscous oil, which was purified by column chromatography on silica gel. Elution with 1 % methanol-chloroform gave (8)(770 mg, 90 %) as a colorless viscous oil: IR(Nujol) 3400∿3250, 1620 cm^{-1}; NMR($CDCl_3$) δ 0.83(3H, t, J=7.0 Hz), 1.03∿2.33(10H, m), 2.40∿3.16(7H, m, 1H disapp. with D_2O), 3.16∿3.83(4H, m), 4.05(1H, t, J=7.0 Hz), 6.05(1H, br.s, disapp. with D_2O), 7.03∿7.76(5H, m), 8.80(1H, br.s, disapp. with D_2O), MS m/e 420(M^+), 143 (100 %).

Anal. ($C_{22}H_{32}N_2O_2S_2 \cdot H_2O$) C, H, N, S.

αH-Lactam(9a) and βH-Lactam(9b) A mixture of (8)(2.87 g, 6.83 mmol), methyl iodide(15.4 ml, 246 mmol) and water(28.9 ml, 1.60 mmol) in acetonitrile(154 ml) was stirred under N_2 at room temperature for 7 days. Most of excess methyl iodide and the solvent were removed in vacuo and the residue was extracted with methylene chloride. The extract was washed with water, 1% $Na_2S_2O_3$, and saturated NaCl, and dried over Na_2SO_4. Removal of the solvent in vacuo afforded a pale brown viscous oil(1.66 g), which was purified by column chromatography on silica gel. Elution with 2% methanol-chloroform gave the βH-lactam(9b)(380 mg, 17.8 %) as a pale yellow foam. Analytical sample was crystallized from n-hexane to give colorless crystals: mp 124∿128 °C; IR($CHCl_3$) 3360, 3250, 1620 cm^{-1}; NMR($CDCl_3$) δ 0.93(3H, t, J=7.0 Hz), 4.70∿5.50(2H, m), 7.05∿7.70(4H, m), 9.10(1H, br.s, disapp. with D_2O); MS m/e 312(M^+, 100 %).

Anal. Calcd. for $C_{19}H_{24}N_2O_2$: m/e 312.1838 Found: m/e 312.1844.

Further elution with 2% methanol-chloroform gave the αH-lactam(9a)(830 mg, 38.9 %) as a pale yellow foam. Analytical sample was crystallized from n-hexane to give colorless crystals: mp 195∿197 °C; IR($CHCl_3$) 3380, 3220, 1600 cm^{-1}; NMR($CDCl_3$) δ 1.02(3H, t, J=7.0 Hz), 4.80∿5.30(2H, m), 7.10∿7.70(4H, m), 9.10(1H, br.s, disapp.

with D_2O). The mass spectrum was similar to that displayed by the βH-lactam(9b).

Anal. Calcd. for $C_{19}H_{24}N_2O_2$: m/e 312.1836 Found: m/e 312.1815.

αH-Amino Alcohol(10a) To an ice-cold solution of (9a)(265 mg, 0.85 mmol) in tetrahydrofuran(50 ml) under N_2 was added a solution of lithium aluminum hydride in tetrahydrofuran(0.85 M, 10 ml, 8.50 mmol). After refluxing for 2 h, the reaction mixture was cooled in an ice bath and treated carefully with concd. NH_4OH. The resulting sludge was filtered through Celite and the residue was washed with methylene chloride. The combined filtrate was washed with saturated NaCl and dried over K_2CO_3. Removal of the solvent in vacuo afforded a pale yellow crystalline residue(240 mg), which was recrystallized form benzene to give (10a)(210 mg, 83.0 %) as pale yellow crystals: mp 165∿168 °C; IR(Nujol) 3350 cm^{-1}; NMR($CDCl_3$+CD_3OD) δ 0.93(3H, t, J=7.0 Hz), 7.00∿7.66(4H, m), 9.70(1H, br.s, disapp. with D_2O); MS m/e 298(M^+, 100 %).

Anal. ($C_{19}H_{26}N_2O$) C, H, N.

βH-Amino Alcohol(10b) βH-Lactam(9b)(165 mg, 0.53 mmol) was reduced in the same manner as αH-lactam(9a). The work up afforded a yellow viscous oil(155 mg), which was purified by column chromatography on silica gel. Elution with chloroform afforded pale yellow crystals which were recrystallized from methanol-ether to give *(10b)(90 mg, 57.0 %) as pale yellow crystals: mp 160∿164 °C; IR(Nujol) 3350∿3200 cm^{-1};* NMR($CDCl_3$+CD_3OD) δ 0.90(3H, t, J=7.0 Hz), 4.46(1H, br.s), 7.00∿7.70(4H, m), 8.86(1H, br.s, disapp. with D_2O). The mass spectrum was similar to that displayed by the αH-amino alcohol(10a).

Anal. Calcd. for $C_{19}H_{26}N_2O$: m/e 298.2044 Found: m/e 298.2019.

(±)-20αH-Dihydrocleavamine(1) To a mixture of (10a)(120 mg, 0.40 mmol) and triethylamine(1.6 ml) in chloroform(3.2 ml) with cooling in an ice bath under N_2 was added methanesulfonyl chloride(0.22 ml, 2.84 mmol), and the reaction mixture was stirred for 2.5 h. Most of the excess methanesulfonyl chloride, triethylamine and chloroform were removed in vacuo at room temperature. The residue was treated with concd. NH_4OH with cooling in an ice bath, and was extracted with chloroform. The extract was dried over Na_2SO_4 and concentrated in vacuo below 40 °C. The residue was dissolved in chloroform(18 ml) and the solution was refluxed under N_2 for 4 h. The solvent was removed in vacuo and the residue was washed with ether, and the residue was dried using an oil pump at room temperature to give the quaternary salt (11a)(126 mg) as a pale yellow hygroscopic amorphous foam.

A solution of the crude quaternary salt(11a)(126 mg) in ethanol(1.5 ml) was transferred to a three-necked flask fitted with a dry ice condenser and ammonia

outlet. After condensing liquid ammonia(60 ml) into the flask, freshly cut sodium metal was added in small pieces until the blue color persisted for 20 min. After stirring for 20 min, the reaction was quenched by addition of NH_4Cl and ammonia was allowed to evaporate. The residue was treated with water and extracted with methylene choride. The extract was washed with water and saturated NaCl and dried over K_2CO_3. Removal of the solvent in vacuo afforded a brown oil(70 mg). Preparative thin-layer chromatography on silica gel gave 20αH-dihydrocleavamine(1)(33 mg, 29.3 % from 10a) as a pale yellow gum[3]: IR(neat) 3360, 2750 cm^{-1}; NMR($CDCl_3$) δ 0.78(3H, t, J=7.0 Hz), 7.00∿7.60(4H, m), 7.78(1H, br.s, disapp. with D_2O). The mass spectrum was identical with the authentic data[2b].

(±)-20βH-dihydrocleavamine(2) βH-Amino alcohol(10b)(90 mg, 0.30 mmol) was mesylated in the same manner as the αH-amino alcohol(10a). The work up afforded the quaternary salt(11b)(45 mg) as a pale yellow hygroscopic amorphous foam.

When the isomeric crude quaternary salt(11b)(45 mg) was treated under the same condition as (11a), the work up afforded a brown oil(35 mg). Preparative thin-layer chromatography on silica gel gave 20βH-dihydrocleavamine(2)(25 mg, 29.5 % from 10b) as a pale yellow gum[3,4b]: IR(neat) 3360, 2760 cm^{-1}; NMR($CDCl_3$) δ 0.88(3H, t, J=7.0 Hz), 7.00∿7.58(4H, m), 7.82(1H, br.s, disapp. with D_2O). The mass spectrum was identical with that of (1). This compound was identical spectroscopically and chromatographically(tlc) with the authentic specimen prepared by an established route.[4b]

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