Synthesis of Pyrroloazepines. Facile Synthesis of 2-Substituted Pyrrole Derivatives by the Phosgene Method

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A highly convenient method for the synthesis of 2-substituted pyrrole derivatives **7a-c** from pyrrole using phosgene was developed. Successively, 7-methyl-6,7-dihydro-1*H*,5*H*-pyrrolo[2,3-*c*]azepine-4,8-dione **1a** and 6,7-dihydro-1*H*,5*H*-pyrrolo[2,3-*c*]azepine-4,8-dione **1b** (aldisin) were synthesized by phosphorus pentoxide/methanesulfonate and polyphosphoric acid cyclization.

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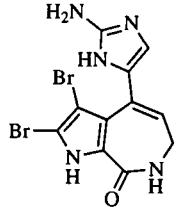
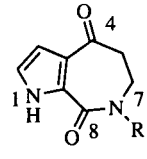
Stevensine, is a natural marine product isolated from Micronesian sponges by Faulkner [1]. It contains a pyrroloazepine skeleton, 6,7-dihydro-1*H*-pyrrolo[2,3-*c*]azepin-8-one, and exhibits hypotensive activity. Initially, it was assumed that aldisin [2] could be used as a basic compound for novel drugs as well as for the synthesis of stevensine-related compounds. We recently synthesized a series of antihypertensive agents (α_1-blocker/serotonin 2 antagonists) with this interesting skeleton [3]. We then attempted to find a more efficient procedure for synthesizing key compounds **1a** and **1b** than the previous procedure [3]. However, a survey of the literature revealed only a few papers on the carbonylation of pyrrole at position-2 [4]. According to the literature, pyrrole-2-carboxylic acid **4** was synthesized from pyrrole *via* a tedious three-step procedure. In brief, acylation of pyrrole with trichloroacetyl chloride gave compound **2**, which was treated with sodium alkoxide to give compound **3**, and then hydrolysis of compound **3** with an aqueous solution of sodium hydroxide afforded compound **4** [4]. In order to obtain intermediate **5** of compounds **1a** and **1b**, additional reaction of compound **4** with oxalyl chloride is required. On the other hand, selective alkoxycarbonylation of position-2 of pyrrole with alkyl chloroformate in the presence of a base could not be achieved, although compound **4** has been prepared from alkyl chloroformate and pyrrolyllithium [5], followed by hydrolysis and decarboxylation of dialkyl pyrrole-1,2-dicarboxylate.

The present paper reports a more efficient method with phosgene for the preparation of pyrrole-2-carbonyl chloride **5** than the previous procedure [4]. In addition, we report a one-pot method for the synthesis of 3-[methyl-(1*H*-pyrrole-2-carbonyl)amino]propionic acid **8a** and 3-[(1*H*-pyrrole-2-carbonyl)amino]propionic acid **8b** from pyrrole, followed by construction of a pyrroloazepine skeleton with phosphorus pentoxide/methanesulfonic acid. Our direct method of synthesizing compound **5** from pyrrole is of economic benefit because pyrrole is less expensive than pyrrole-2-carboxylic acid [6].

Slow addition of a solution of phosgene monomer, dimer, or trimer in toluene to a stirred solution of pyrrole and *N,N*-dimethylaniline or *N,N*-diethylaniline in toluene was carried at 0° out to give compound **5** [7]. Subsequently, a mixed solution of ethyl 3-(methylamino)propionate **6a** [8] in *N,N*-dimethylaniline or triethylamine was added to the reaction mixture at 0°. Then the mixture was stirred at 110° (in the case of *N,N*-dimethylaniline) or at room temperature (in the case of triethylamine) for 1 hour to give ethyl 3-[methyl-(1*H*-pyrrole-2-carbonyl)-amino]propionate **7a**, which was successively treated with a 10% aqueous solution of sodium hydroxide to afford 3-[methyl-(1*H*-pyrrole-2-carbonyl)amino]propionic acid **8a**. Thus, this efficient one-pot reaction converted pyrrole into compound **8a** in a 68-75% yield. Similarly, β-alanine methyl ester **6b** or 3-(methylamino)propionitrile **6c** as well as compound **6a** was added to compound **5** in the reaction solution to give methyl 3-[methyl-(1*H*-pyrrole-



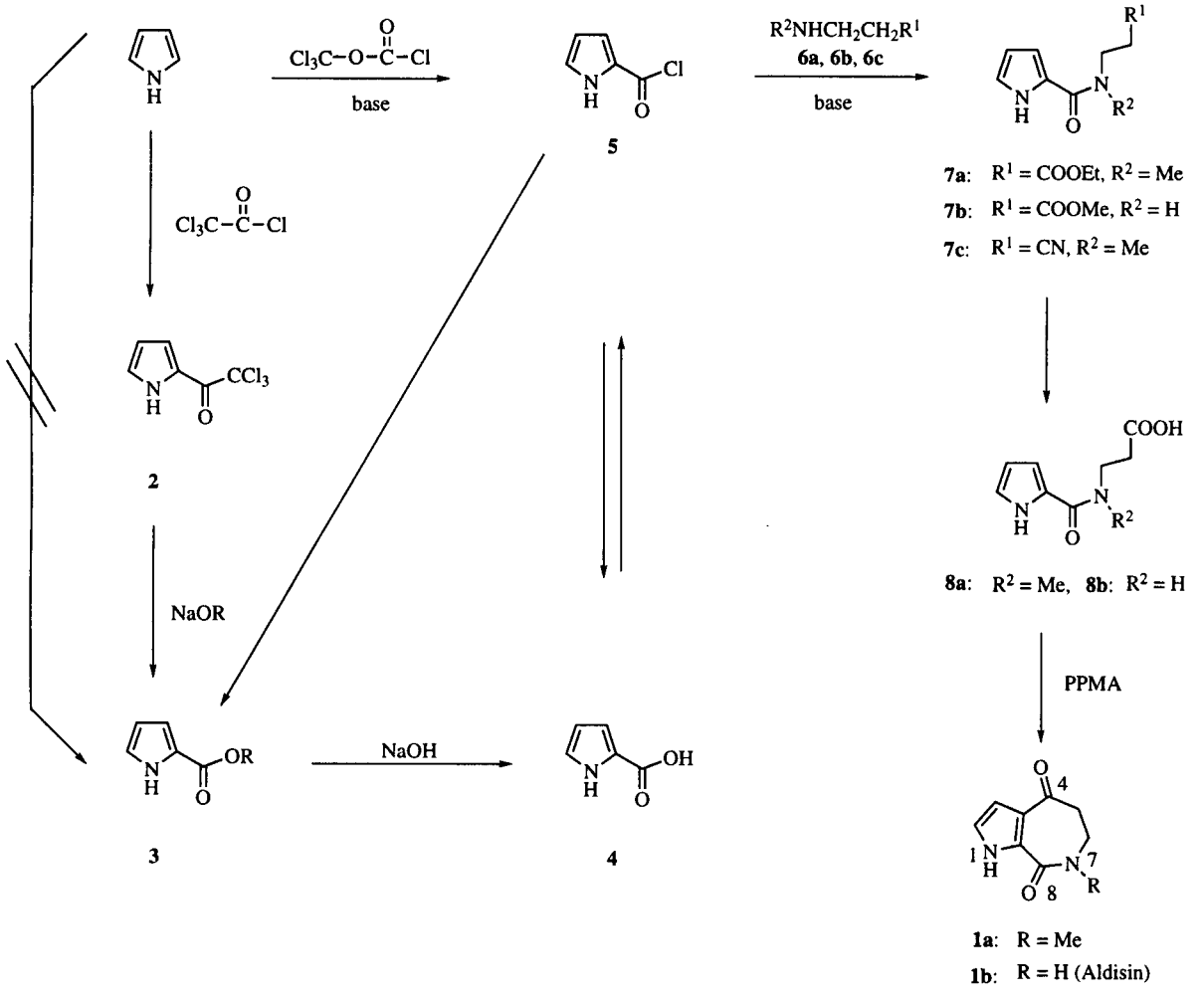
Stevensine



1a: R = Me
1b: R = H (Aldisin)

Figure

Scheme



2-carbonyl)amino]propionate **7b** or 1*H*-pyrrole-2-carboxylic acid (2-cyanoethyl)methylamide **7c**, respectively. Hydrolysis of **7c** with a 10% aqueous solution of hydrogen chloride afforded a compound which was identical to compound **8a**. An alternative method for preparation of pyrrole-2-carboxylic acid **4** was the reaction of compound **5** derived from pyrrole with an aqueous solution of sodium hydroxide. We carefully compared product **4** obtained by the phosgene method with the authentic sample obtained by the reported procedure [4] and found it to be identical by nmr spectroscopy. The other isomer, pyrrole-3-carboxylic acid, was not detected at all in the nmr spectrum. Similarly, methyl pyrrole-2-carboxylate **3** was easily obtained by treatment of compound **5** with sodium methylate in methanol. As mentioned above, the phosgene method was found to be useful for producing 2-substituted pyrrole derivatives. Instead of using poisonous phosgene gas or its toluene solution, one can perform a series of reactions with phosgene dimer (trichloromethyl chloroformate, a liquid) [9] or phosgene trimer [bis(trichloromethyl)carbonate, a solid] [10]. We also investigated a suitable base and found that *N,N*-dimethylaniline was most desirable. When we used triethylamine, pyridine, or *N,N,N,N*-tetramethylurea [11] instead, the yield of compound **8a** was far lower.

Finally, 7-methyl-6,7-dihydro-1*H*,5*H*-pyrrolo[2,3-*c*]-azepine-4,8-dione **1a** and 6,7-dihydro-1*H*,5*H*-pyrrolo-[2,3-*c*]azepine-4,8-dione (aldisin) **1b** were synthesized from compounds **8a** and **8b** using 75-80% polyphosphoric acid at 100° for 30 minutes or more effectively using a mixed solution of methanesulfonic acid and phosphorus pentoxide at 80° for 10 minutes or 100° for 3 minutes. The mixed solution could be prepared at 80-100° within 10-60 minutes. The resulting solution was employed *in situ* for the cyclization (phosphorus pentoxide/methanesulfonic acid: substrate = 10:1.5-2.0 weight ratio), (see Experimental). Cyclization with the solution was found to proceed more quickly than with polyphosphoric acid.

Moreover, it could be employed even on a large scale preparation since it handled easily because of a liquid. Therefore, the cyclization with phosphorus pentoxide/-methanesulfonic acid should be applied to other synthesis of heterocycles. In summary, an effective method for the synthesis of 2-substituted pyrrole derivatives (alkyl pyrrole-2-carboxylate **3**, pyrrole-2-carboxylic acid **4**, and *N*-mono or dialkyl pyrrole-2-carboxamide **7**) from pyrrole and phosgene was established. This procedure could be applied to the synthesis of other 2-substituted pyrroles. In addition, pyrroloazepine derivatives **1a** and **1b** were synthesized from compound **8** with phosphorus pentoxide/-methanesulfonic acid or polyphosphoric acid.

EXPERIMENTAL

Melting points were determined with a Yanagimoto micro-melting point apparatus and are uncorrected. The ^{1}H nmr spectra were recorded with a JEOL GX-270 (270 MHz) spectrometer in a deuteriochloroform solution with tetramethylsilane as the internal standard, unless otherwise noted. The ir spectra were obtained using a Hitachi 260-10 infrared spectrometer. Thin layer chromatography was carried out on Merck silica gel plates (60F-254) and column chromatography was performed on Merck silica gel (70-230 mesh).

Preparation of Ethyl 3-(Methylamino)propionate (**6a**).

Ethyl acrylate (519 ml, 4.80 moles) was slowly added over 1 hour to a stirred solution of mono methylamine (238 g, 7.68 mmoles) in ethanol (700 ml) at 0°. After 30 minutes, the solution was warmed to room temperature and stirred for 1-2 hours. Direct distillation yielded oily compound **6a** (264 g, 42%), bp 60°/10 mm Hg.

Use of excess monomethylamine yielded a certain by-product with bis[2-(ethoxycarbonyl)ethyl]methylamine as a distillation residue. Reverse addition of two reagents did not improve the yield.

Preparation of 3-(Methylamino)propionitrile **6c.**

Acrylonitrile (23.7 ml, 0.36 mmole) was added to a stirred solution of monomethylamine 13.4 g (0.43 mmole) in methanol (48 ml) over 15 minutes at 0°. After 1 hour, the solution was warmed to room temperature and stirred overnight. Direct distillation afforded compound **6c** (25.07 g, 84%), bp 81°/24 mm Hg.

1A) Synthesis of 3-[Methyl-(1*H*-pyrrole-2-carbonyl)amino]propionic Acid **8a.**

A solution of phosgene dimer (54 ml, 450 mmoles) in toluene (400 ml) was added to a stirred solution of pyrrole (60.3 g, 900 mmoles) and *N,N*-dimethylaniline (108.9 g, 900 mmoles) in toluene (1 ℓ) over 20 minutes at 0°. After stirring for 5 minutes at 0°, the mixture was stirred at room temperature for 2 hours. After cooling at 0°, a mixed solution of **6a** (141.5 g, 1080 mmoles) and *N,N*-dimethylaniline (130.7 g, 1080 mmoles) in toluene (300 ml) was added with stirring. After 5 minutes, the solution was gently refluxed for 1 hour and toluene was removed at 40-50° under reduced pressure to give dark brown residue **7a**. Both ethanol (600 ml) and a 10% aqueous solution of sodium hydroxide (1.5 ℓ) were added at 0° and stirred for 20 minutes. Then the mixture was warmed to room temperature and stirring was continued for 18 hours. To the reaction mixture were added chloroform (2 ℓ) and sodium chloride (80 g). The mixture was filtered through 'Celite-Nutze' (5 mm thick). The filtrate was shaken, and the chloroform layer (1 ℓ) was discarded. Additional chloroform (1 ℓ) and sodium chloride (20 g) were added to the aqueous layer and separated. This operation was repeated twice. Then the aqueous layer was acidified (*p*H 3-4) with 10% hydrochloric acid (350 ml of concentrated hydrochloric acid in 1.1 ℓ of water) and immediately extracted three times with ethyl acetate (total 4 ℓ). The ethyl acetate layer was dried over anhydrous magnesium sulfate (300 g) and activated charcoal powder (30-40 g) (Wako KK Code #037-02115) was added. After filtration and evaporation, light brown crystals were obtained (132.6 g, 75%). The crystals were dissolved in methanol (1 ℓ) at 40-50°. The solution was concentrated under reduced pressure to a 1/3rd volume and isopropyl ether (500 ml) was added. Recrystallization gave colorless crystals of **8a** (120 g, 68%) after drying at 50° under reduced pressure, mp 123-124°; ir (Nujol): 3200, 1700, 1570 cm^{-1}; ^{1}H nmr (deuteriochloroform, δ ppm): 2.72 (2H, t, J = 7 Hz), 3.32 (3H, brs), 3.89 (2H, brt), 6.25 (1H, m), 6.40 (1H, brs), 6.96 (1H, brs).

Anal. Calcd. for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 55.28; H, 6.20; N, 14.19.

1B) Synthesis of Compound **8a**.

Similarly, phosgene trimer (triphosgene) was employed instead of the dimer, using 1/3rd molar equivalent of phosgene trimer to 1 molar equivalent of pyrrole. The yield of compound **8a** was the same as that with synthetic method 1A.

1C) Synthesis of **8a**.

A solution of phosgene dimer (54 ml, 450 mmoles) in toluene (400 ml) was added to a stirred solution of pyrrole (60.3 g, 900 mmoles) and *N,N*-dimethylaniline (108.9 g, 900 mmoles) in toluene (1 ℓ) over 20 minutes at 0°. After stirring for 2 hours at 0°, a solution of **6a** (141.5 g, 1080 mmoles) and triethylamine (90.9 g, 900 mmoles) in toluene (200 ml) was added to the stirred solution, and the mixture was stirred for 30 minutes. After filtration of triethylamine hydrochloride and washing the salt with toluene (200 ml), the toluene was removed from the filtrate under reduced pressure. To the residual oil **7a** were added ethanol (200 ml) and 3.75 *M* aqueous sodium hydroxide (1 ℓ) at 0°, and the mixture was stirred at room temperature for 18 hours. The reaction mixture was extracted with chloroform (1000 ml, 500 ml, and 500 ml) and the aqueous layer was made acidic (*p*H 3-4) with 17.5% hydrochloric acid (500 ml). Immediately (otherwise, the crude crystals began to precipitate), the aqueous layer was extracted with ethyl acetate (1000 ml, 500 ml, and 500 ml). The ethyl acetate layer was dried over anhydrous magnesium sulfate (200 g), and decolorized with activated charcoal powder (30 g) (Wako KK, Code #037-02115). After filtration and evaporation, almost colorless crystals (150 g) were obtained. Similarly, recrystallization was carried out to give compound **8a** (120 g, 68%).

2) Synthesis of 3-[(1*H*-Pyrrole-2-carbonyl)amino]propionic Acid **8b**.

A solution of phosgene dimer (4.5 ml, 37.25 mmoles) in toluene (30 ml) was added over 20 minutes to a stirred solution of pyrrole (5 g, 74.5 mmoles) and *N,N*-dimethylaniline (9.4 ml,

74.5 mmoles) in toluene (70 ml) at 0°. Then the solution was stirred at 0° for 2 hours and at room temperature for 1 hour. In another flask, triethylamine (26 ml, 186 mmoles) was added to a stirred suspension of β-alanine methyl ester hydrochloride (12.5 g, 89.4 mmoles) in methylene chloride (60 ml). The mixture was stirred at room temperature for 30 minutes and then added over 20 minutes at 0° to the solution of compound **5** prepared as described above. The resulting mixture was stirred for 1 hour. After filtration of the precipitate, the filtrate was concentrated to give a residue, which was dissolved in ethyl acetate. The solution was washed with a saturated aqueous solution of sodium bicarbonate and then water, dried over anhydrous magnesium sulfate, and evaporated to give methyl 3-[methyl-(1*H*-pyrrole-2-carbonyl)amino]propionate **7b** (9.5 g, 65%).

A mixture of compound **7b** (9.5 g, 48.5 mmoles) and 3.75 *N* sodium hydroxide (100 ml) in ethanol (20 ml) was stirred at room temperature. After 18 hours, the reaction mixture was washed with chloroform (30 ml). The aqueous layer was acidified with a 10% aqueous solution of hydrogen chloride and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and decolorized with activated charcoal powder (Wako KK, Code #037-02115). Then the solution was evaporated to give compound **8b** (6.8 g, 50%), mp 149-150° (lit [2], mp 150°, from ethyl acetate-ether).

Anal. Calcd. for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.70; H, 5.66; N, 15.46.

3A) Synthesis of 1*H*-Pyrrole-2-carboxylic Acid (2-Cyanoethyl)-methylamide **7c**.

Using method 1A, 2.48 g of 3-(methylamino)propionitrile **6c** was employed instead of ethyl 3-(methylamino)propionate **6a**, to give compound **7c** (2.65 g, 51%), mp 106-107°; ir (chloroform): 2250, 1600 cm^{-1}; ^1H nmr (deuteriochloroform): 2.74 (2H, t, J = 7 Hz), 3.45 (3H, s), 3.82 (2H, t, J = 7 Hz), 6.30 (1H, m), 6.62 (1H, brs), 6.98 (1H, brs).

Anal. Calcd. for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.71. Found: C, 61.04; H, 6.12; N, 23.60.

3B) Synthesis of Compound **8a** from Compound **7c**.

To a solution of compound **7c** (2.65 g in 5 ml of dioxane) was added a 10% aqueous solution of hydrogen chloride (5 ml) and the mixture was refluxed for 1 hour. To the reaction mixture were added a 10% aqueous solution of sodium hydroxide and ethyl acetate, and the organic layer was removed after extraction. The basic solution was acidified with 10% hydrochloric acid solution and extracted three times with ethyl acetate. Then the organic layer was dried over anhydrous magnesium sulfate, filtered, and evaporated to give compound **8a** (1.65 g, 60%), which was identified with compound **8a** prepared by method 1.

4) Preparation of Pyrrole-2-carboxylic Acid **4**.

A solution of phosgene dimer (0.9 ml, 7.5 mmoles) in toluene (8.5 ml) was added to a stirred solution of pyrrole (1.0 g, 14.9 mmoles) and *N,N*-dimethylaniline (1.82 g, 15.0 mmoles) in toluene (21.5 ml) over 10 minutes at 0°. Then the mixture was stirred at room temperature for 18 hours and refluxed for 2 hours. After cooling to 0°, the mixture was quenched with 10% sodium hydroxide and extracted with chloroform The aqueous layer was weakly acidified with 10% hydrochloric acid solution and extracted with ethyl acetate. Then the organic layer was dried over anhydrous magnesium sulfate, filtered, and evaporated to give pale yellow crystals (1.1 g, 67%). The crystals were identified by comparison with an authentic sample.

5) Preparation of Methyl Pyrrole-2-carboxylate **3**.

Similarly, methyl pyrrole-2-carboxylate **3** was prepared by addition of 28% sodium methoxide/methanol to the reaction mixture (described in Experimental 1A) before quenching with water. Thus, 28% sodium methoxide/methanol (8 ml) was added to pyrrole-2-carbonyl chloride **5** in the reaction mixture at 0° and stirring was continued at room temperature for 1 hour. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and evaporated under reduced pressure to give the residue, which was purified by silica gel chromatography to give compound **3** (886 mg, 84%), which was identified by comparison with an authentic compound.

6) Synthesis of 7-Methyl-6,7-dihydro-1*H*,5*H*-pyrrolo[2,3-*c*]azepine-4,8-dione **1a.**

Phosphorus pentoxide (54 g, 0.38 mole) was added to methanesulfonic acid (546 g, 5.69 moles) and the mixture was stirred vigorously at 80° for 1 hour. To the resulting colorless solution of polyphosphoric acid/methanesulfonic acid, was added the colorless crystals of compound **8a** (100 g, 0.51 mole) were added all at once at 80°. After 10 minutes, the reaction solution was poured into ice-water (1000 ml). (No exothermic reaction occurred at this operation.) The mixture was extracted three times with chloroform (600, 400, and 400 ml) and the organic layer was washed once with a 0.5% aqueous solution of sodium bicarbonate (400 ml), dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give colorless needles of pyrroloazepine **1a** (74 g, 82%), mp 175-177° (from chloroform/ethyl acetate or chloroform/isopropyl ether; ir (chloroform): 3425, 1665, 1620 cm^{-1}; ^1H nmr (δ, ppm, 270 MHz): 2.89 (2H, m), 3.27 (3H, s), 3.73 (2H, m), 6.77 (1H, t, J = 2.6 Hz), 6.94 (1H, t, J = 2.6 Hz), 10.84 (1H, brs).

Anal. Calcd. for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.61; H, 5.76; N, 15.66.

7) Synthesis of 7-Methyl-6,7-dihydro-1*H*,5*H*-pyrrolo[2,3-*c*]azepine-4,8-dione **1a**.

Phosphorus pentoxide (40.0 g, 282 mmoles) was added to 75% polyphosphoric acid (160 g) and the mixture was vigorously stirred for 1 hour at 100°. To the mixture were added crystals of compound **8a** (20.0 g, 102 mmoles) all at once at 100°. Then the viscous mixture was stirred vigorously at the same temperature for 30-60 minutes. After cooling the flask to room temperature, the reaction mixture was poured into ice-water (500 ml). (An exothermic reaction occurred. The reaction flask was washed with ice-water and the solution was combined with the above mentioned solution.) The combined solution was extracted with chloroform (500 ml x 3) and the organic layer was washed with brine (500 ml), dried over anhydrous magnesium sulfate (50 g), and evaporated to give pyrroloazepine **1a** (15.9 g, 87%).

8) Synthesis of 6,7-Dihydro-1*H*,5*H*-pyrrolo[2,3-*c*]azepine 4,8-dione **1b**.

Phosphorus pentoxide (0.2 g, 1.4 mmoles) was added to 75% polyphosphoric acid (30 g) and the mixture was vigorously stirred for 40 minutes at 120°. To the mixture were added crystals of compound **8b** (5.0 g, 27 mmoles) all at once at 100°. Then the viscous mixture was stirred vigorously at the same

temperature for 20 minutes. After cooling the flask to room temperature, the reaction mixture was poured into ice-water and a 10% aqueous solution of sodium hydroxide was added to make the solution *p*H 6.5-7.0. The precipitate was filtered off and the filtrate was extracted four times with ethyl acetate (**1b** was a water-soluble compound), after which the organic layer was dried over anhydrous magnesium sulfate and evaporated to give compound **1b** (2 g, 44%). The crude crystals (2 g) were dissolved in *N,N*- dimethylformamide (8-10 ml) at 100° and ethanol (2 ml) was added to the solution at 0°. The resulting crystals were washed with a cold solution of *N,N*-dimethylformamide-ethanol (3:1) and dried for 5 hours at 50°. Aldisin **1b** (1.1 g) was obtained as colorless crystals, mp 270-272° (from *N,N*-dimethylformamide/ethanol); ir (potassium bromide): 3214, 1662, 1638 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6) (δ) 2.70 (2H, m), 3.36 (2H, m), 6.55 (1H, d, J = 2.6 Hz), 6.98 (1H, d, J = 2.6 Hz), 8.31 (1H, t, J = 4.0 Hz), 12.14 (1H, brs).

Anal. Calcd. for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.41; H, 5.09; N, 17.15.

REFERENCES AND NOTES

[1] K. F. Albizati and D. J. Faulkner, *J. Org. Chem.*, **50**, 4163 (1985).

[2] F. J. Schmitz, S. P. Gunasekera, V. Lakshmi and L. M. V. Tillekeratne, *J. Nat. Prod.*, **48**, 47 (1985); R. H. Prager and C. Tsopelas, *Aust. J. Chem.*, **43**, 367 (1990); *idem., ibid.*, **45**, 1771 (1992).

[3] A. Mizuno, H. Cho, M. Miya, T. Tatsuoka and T. Ishihara, Japan Patent H2-26137 (1990); *Chem. Abstr.*, **119**, P160316m, (1993).

[4] D. M. Bailey, R. E. Johnson and N. F. Albertson, *Org. Synth.*, **51**, 100 (1971); J. W. Harbuck and H. Rapoport, *J. Org. Chem.*, **37**, 3618 (1972).

[5] A. Treibs and A. Dietl, *Liebigs Ann. Chem.*, **619**, 80 (1958).

[6] Pyrrole-2-carboxylic acid is a useful pharmaceutical building block that is commercially available but is very expensive. Therefore, it cannot be used on a large-scale.

[7] The reverse addition of pyrrole to phosgene solution was also found to give pyrrole-2-carbonyl chloride **5**, because chemical conversion to compound **8a** occurred with a similar yield.

[8] K. Schloegl and R. Schloegl, *Monatsh. Chem.*, **95**, 922 (1964); *Chem. Abstr.*, **61**, 11995f (1964).

[9] A commercially available reagent obtained from Hodogaya Chemical Co. Ltd., Tokyo.

[10] A commercially available reagent obtained from Aldrich Chemical Company, Inc., Milwaukee.

[11] M. S. Newman and L. K. Lala, *Tetrahedron Letters*, **34**, 3267 (1967).