Facile Stereoselective Synthesis of (+)- and (−)-Allocoronamic Acids

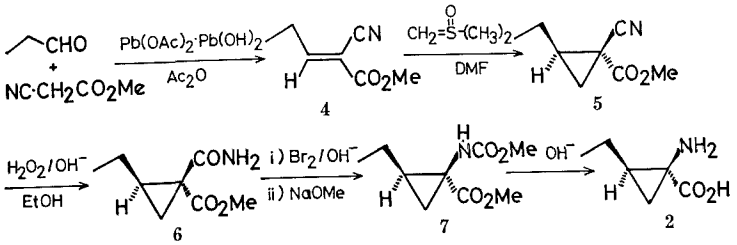
Kunio SHIRAISHI, Akitami ICHIHARA* and Sadao SAKAMURA

Department of Agricultural Chemistry, Faculty of Agriculture, Hokkaido University, Sapporo 060, Japan

Received October 3, 1977

In the previous papers, the structure[1] and absolute configuration[2] of coronatine (**1**) which was isolated from a pathogenic bacterium responsible for chocolate spot disease of italian ryegrass, have been reported. Recently coronatine was proved to be a vivotoxin.[3] In order to investigate the physiological activities and structure relationship, synthesis of stereoisomers of coronamic acid (**3a**) was conducted. This paper describes the stereoselective synthesis and optical resolution of (±)-allocoronamic acid (**2**).

(±)-Allocoronamic acid (**2**) was synthesized stereoselectively as shown in Scheme 1. Commercially available reactants, propionaldehyde and methyl cyanoacetate were condensed in acetic anhydride in the presence of the catalyst, basic lead acetate[4] and the *E*-methyl propylidene cyanoacetate (**4**), bp 102°C (16 mmHg), IR ν_{max}^{film} cm^{-1}; 2230, 1740, 1630, 760, PMR; $\delta_{TMS}^{CDCl_3}$ 1.18 (3H, t, J=7Hz, CH_3), 2.60 (2H, q, J=7Hz, $-CH_2-$), 3.89 (3H, s, $-OCH_3$), 7.69 (1H, t, J=8Hz, ⩘H), MS *m/e*: 139 (M^+), 80, 53, was obtained in 45% yield. The Micheal-type cyclopropanation of **4** with dimethyloxosulfonium methylide in dimethyl formamide[5] afforded a cyclopropane methylester **5** in 63% yield. A number of procedures for the amidation of **5** (*e.g.* active MnO_2, $TiCl_2$/AcOH, conc. H_2SO_4, $Hg(OAc)_2$/AcOH. *etc.*) were attempted, but the desired amide was obtained in less than 10% yield. The best yield (20%) was attained by successive treatments (three times) of **5** with alkaline hydrogen peroxide.[6] The amide **6** has the following physicochemical properties, mp 81~85°C, IR ν_{max}^{KBr} cm^{-1}: 3410, 3210, 1720, 1670, 1590, PMR $\delta_{TMS}^{CDCl_3}$: 0.95 (3H, t, J=7Hz, CH_3), 1.1~2.0 (5H, m.), 3.68 (3H, s, OCH_3), 5.82, 8.12 (each 1H, br. s, NH_2), MS *m/e*: 171 (M^+), 154, 122. The PMR signal of methylester group (δ 3.68) in **6** can be sharply distinguished from that of the diastereomer[2] (δ 3.75) because of the deshielding effect of the ethyl group in the latter. This fact indicates that the amide group is oriented *cis* to the ethyl group, and the precursor **4** should also have the *E*-configuration, although the geometrical isomerism has not been discussed in detail in earlier reports.[7] The Hofmann degradation of **6** was carried out in two steps, N-bromination and subsequent rearrangement of carbon-nitrogen bond in sodium methoxide. The resultant urethane **7** had; mp 67.5~69.0°C, IR ν_{max}^{KBr} cm^{-1}; 3360, 1740, 1710, 1525; PMR $\delta_{TMS}^{CDCl_3}$; 1.02 (3H, t, J=7Hz, CH_3), 0.8~1.9 (5H, m.), 3.73 (6H, s, 2×OCH_3), 5.21 (1H, br. s, NH), MS *m/e*: 201 (M^+), 169, 82. (±)-Allocoronamic acid (**2**) was obtained by hydrolysis of **7** with sodium hydroxide and recrystallized from water-acetone to give **2** as glassy crystals in 81% yield. The compound **2** sublimes at 184~185°C, and has the following physicochemical properties, Found: C, 55.76;



SCHEME 1. Synthetic Route of (±)-Allocoronamic Acid (**2**)

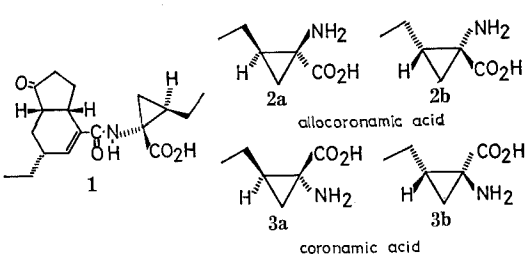


FIG. 1. Absolute Configuration of Coronatine (**1**) and Amino Acids.

H, 8.58; N, 10.82. Calcd. for $C_6H_{11}O_2N$: C, 55.79; H, 8.58; N, 10.85%, MS *m/e*: 129 (M^+), 100, 54, IR ν_{max}^{KBr} cm^{-1}: 3425, 1645, 1580, 1420, PMR $\delta_{MeOH}^{D_2O}$: 1.06 (3H, t, J=7Hz, CH_3), 0.85~1.90 (5H, m.).

The synthesized (±)-allocoronamic acid was resolved through the quinine salt. The salts of N-formyl derivatives of **2** were recrystallized fractionally from hot ethyl acetate-ethanol. The less soluble salt was hydrolyzed to yield (+)-allocoronamic acid (**2a**); $[\alpha]_D^{23}$+65.0° (c=1.83, H_2O). The salt recovered from the mother liquor was recrystallized from acetone to yield the antipode (**2b**); $[\alpha]_D^{21}$−68.4° (c=1.15, H_2O). The absolute configurations of these compounds were assigned from the application of sector rule[2] in ORD. The extrema of molecular rotations in **2a** and **2b** are $[\phi]_{233}^{26}$+702° ($c=2.5\times10^{-3}$, H_2O) and $[\phi]_{233}^{26}$ −722° ($c=2.5\times10^{-3}$, H_2O), respectively. And so **2a** and **2b** were depicted as (+)-(1*S*, 2*R*)-1-amino-2-ethylcyclopropane-1-carboxylic acid and (−)-(1*R*, 2*S*)-1-amino-2-ethylcyclopropane-1-carboxylic acid, respectively as shown Fig. 1.

The partial synthesis of coronatine isomers from (+)- and (−)-allocoronamic acids and coronafacic acid, and the stereochemical contribution of coronamic acid moiety in **1** to induce the physiological activities is being investigated.

REFERENCES

1) A. Ichihara, K. Shiraishi, H. Sato, S. Sakamura, K. Nishiyama, R. Sakai, A. Furusaki and T. Matsumoto, *J. Am. Chem. Soc.*, **99**, 636 (1977).
2) A. Ichihara, K. Shiraishi, S. Sakamura, K. Nishiyama and R. Sakai, *Tetrahedron Lett.*, **1977**, 269.
3) K. Nishiyama, R. Sakai, A. Ezuka, A. Ichihara, K. Shiraishi and S. Sakamura, *Ann. Phytopath. Soc. Japan*, **43**, 219 (1977).
4) I. L. Finar and D. D. Libman, *J. Chem. Soc.*, **1949**, 2726.
5) S. R. Landor and M. Punja, *J. Chem. Soc.* (*C*), **1967**, 2495.
6) C. A. Buehler and D. E. Pearson, "Survey of Organic Synthesis," John Wiley and Sons Inc., New York, 1970, pp. 903.
7) F. D. Popp and A. Catala, *J. Org. Chem.*, **26**, 2738 (1961).