Synthesis of 1-Aminocyclobutanecarboxylic Acid

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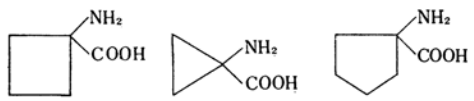
Some alicyclic amino acids have been known as physiologically interesting compounds. 1-Aminocyclopropanecarboxylic acid (II) was prepared by Ingold and his coworkers[1] and



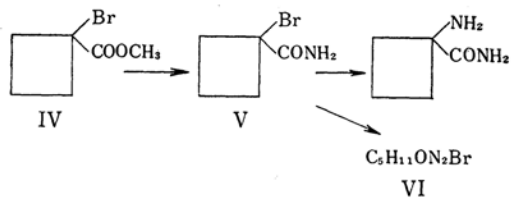
I II III

was recently isolated by Burroughs[2] from apple cider and perry pear juices, and 1-aminocyclopentanecarboxylic acid (III) was reported to show anticancerous action[3,4].

The authors wish to report the synthesis of an additional alicyclic amino acid, 1-aminocyclobutanecarboxylic acid (I) by two methods, the first of which involves reaction of methyl 1-bromocyclobutanecarboxylate (IV) with ammonia and the second involves hydrolysis of 5-cyclobutane-spiro-hydantoin (IX).

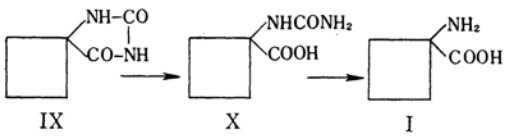
The first attempted method did not afford I, but an isomeric unsaturated amino acid, which was produced by a rupture of the cyclobutane-ring. Although IV[5] was easily converted by ammonium hydroxide into 1-bromocyclobutanecarboxamide (V), amination of V by using potassium phthalimide or hexamethylenetetramine was unsuccessful. When V was heated with aqueous ammonia in a sealed tube, a substance of m. p. 163~164°C was obtained and its analytical values corresponded to the molecular formula of $C_5H_{11}ON_2Br$ (VI). Hydrolysis of VI with a solution of barium hydroxide gave a very hygroscopic amino acid (VII). This amino acid was characterized by conversion into its benzoyl derivative VIII

1) C. K. Ingold et al., *J. Chem. Soc.*, **1922**, 1911.
2) L. F. Burroughs, *Nature*, **179**, 360 (1957).
3) R. B. Ross, *J. Chem. Educ.*, **36**, 368 (1959).
4) T. A. Connors and W. C. J. Ross, *J. Chem. Soc.*, **1960**, 2119.
5) A. Campbell and H. N. Rydon, ibid., **1953**, 3002.



which had the same molecular formula as that of benzoyl derivative of I, but absorbed bromine, indicating the presence of a double-bond.

In the second procedure, partial hydrolysis of 5-cyclobutane-spiro-hydantoin (IX), which was prepared by the method of Ingold[1] et al., afforded 1-uramidocyclobutanecarboxylic acid (X). IX or X was heated with a solution of



barium hydroxide for 24 hr., affording an amino acid, whose paperchromatograph showed a spot of R_f value 0.5 in *n*-butanol/acetic acid/water; (4:1:1). This amino acid was confirmed to be 1-aminocyclobutanecarboxylic acid (I) by elementary analysis and conversion into its benzoyl derivative (XII), which saturated against bromine.

Although the structure of VII was thought to be γ-amino-α-methylcrotonic acid from chemical behavior and infrared spectrum of its benzoyl derivative, it could not be confirmed. In addition, paperchromatograph of VII showed a spot of R_f value 0.50 as main-product, whose benzoyl derivative was isolated and some other two spots of R_f value, 0.30 and 0.10 in *n*-butanol/acetic acid/water; (4:1:1), (Fig. 1). They also seemed to be produced by a rupture of the cyclobutane-ring, but were not isolated.

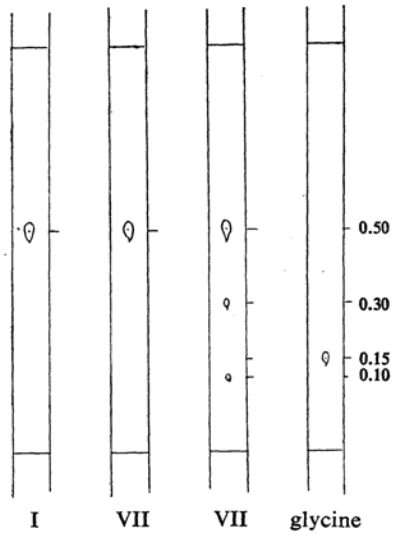


Fig. 1

Experimental

Methyl 1-Bromocyclobutanecarboxylate (IV).—The procedure of Campbell and Rydon[5] was used. Twenty two grams of cyclobutanecarboxylic acid was heated under reflux at 100°C for 1 hr. with 29 g. of thionyl chloride. Red phosphorus (0.25 g.) and 40 g. of bromine were added and heating was continued at 110~120°C for further 3 hr. The reaction mixture was poured into 30 cc. of absolute methanol, and then diluted with water and extracted with ether. After removal of ether, the distillation of the residue gave 30 g. of oil, b. p. 70~75°C/23 mmHg, in a 70% yield.

Found: C, 37.33; H, 4.87; Br, 42.04. Calcd. for $C_6H_9O_2Br$: C, 37.33; H, 4.67; Br, 41.40%.

1-Bromocyclobutanecarboxamide (V).—Twenty six grams of IV was added to 100 cc. of concentrated aqueous ammonia and was continued, stirring for 2 hr. The precipitate was collected and recrystallized from ethanol affording 20 g. of needles, melted at 153~154°C.

Found: C, 33.85; H, 4.64; N, 7.81. Calcd. for C_5H_8ONBr: C, 33.72; H, 4.49; N, 7.87%.

Ammonolysis of V.—Three grams of V was suspended in 30 cc. of concentrated aqueous ammonia and was heated for 6 hr. in a sealed tube. Removal of the solvent from the reaction mixture gave a syrupy residue. When the residue was allowed to stand in an ice bath, a precipitate was formed. After recrystallization from ethanol, 1.5 g. of colorless prisms, m. p. 163~164°C (VI), were obtained.

Found: C, 30.92; H, 5.49; N, 14.11. Calcd. for $C_5H_{11}ON_2Br$: C, 30.77; H, 5.64: N, 14.36%.

Hydrolysis of VI with Barium Hydroxide Solution.—Two grams of VI and 5 g. of barium hydroxide were added to 50 cc. of water and refluxed for 2 hr. The reaction mixture was filtered and to the filtrate was added carbon dioxide gas. After removal of barium carbonate, the solution was concentrated in vacuo resulting a syrupy residue. This syrup was solidified by addition of 30 cc. of absolute ethanol affording a crystalline substance, which was so hygroscopic that its melting point was not determined. The syrup was positive in the ninhydrin-test and its paperchromatograph showed 3 spots of R_f values 0.50, 0.30 and 0.10 in *n*-butanol/acetic acid/water; (4:1:1). (Fig. 1). The syrup, however, was characterized by conversion into its benzoyl derivative VIII, which melted at 183~185°C and absorbed bromine.

Found: C, 65.19; H, 5.77; N, 6.30. Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.39%.

The infrared spectrum showed strong bands at 3400, 1615, 1545 (-NH-CO-), 1695 (-COOH) and 1425 cm^{-1}.

The carboxyl band, shifting toward a lower wave

number, indicates the presence of C=C bond adjacent to the carboxyl group[6]. The band at 1425 cm^{-1}, seemed to be attributed to the CH_2 deformation frequency of the group of $-C=C-CH_2-$[7].

VIII was hydrolyzed by hydrochloric acid giving an amino acid whose paperchromatograph showed only one spot of R_f value 0.50.

5-Cyclobutane-spiro-hydantoin (IX). — The procedure of Ingold et al.[1] was used. This hydantoin melted at 222~225°C (reported m. p. 225°C).

1-Uramidocyclobutanecarboxylic Acid (X).—Two grams of IV and 4 g. of barium hydroxide were added to 50 cc. of water and refluxed for 2 hr. The reaction mixture was filtered and to the filtrate was added carbon dioxide gas. After removal of barium carbonate, the solution was concentrated in vacuo resulting a residue. The residue was recrystallized from ethanol affording 1 g. of colorless m. p. 200~202°C.

Found; N, 17.25. Calcd. for $C_6H_{10}O_3N_2$: N, 17.71%.

1-Aminocyclobutanecarboxylic Acid (I). — Two grams of IV and 5 g. of barium hydroxide ware added to 50 cc. of water and refluxed for 24 hr. The reaction mixture was filtered and to the filtrate was added carbon dioxide gas. After removal of barium carbonate, the solution was concentrated in vacuo resulting a residue. The residue was recrystallized from ethanol-water affording 1 g. of colorless prisms, m. p. 222~225°C (sublime). Paperchromatograph showed a spot of R_f value 0.50 in *n*-butanol/acetic acid/water; (4 : 1 : 1). (Fig. 1). The infrared spectrum showed amino acid bands (2930, 1630, 1520 cm^{-1}).

Found: C, 51.67; H, 7.90; N, 12.15. Calcd. for $C_5H_9O_2N$: C, 52.16; H, 7.88; N, 12.17%.

Benzoyl Derivative of I.—I was converted into a benzoyl derivative by the general method and gave colorless prisms, which melted at 205~206°C and saturated towards bromine. The infrared spectrum showed strong bands at 3280, 1630, 1530 (-CONH-) and 1710 cm^{-1} (-COOH).

Found: C, 65.87; H, 6.18; N, 6.35. Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.39%.

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6) L. J. Bellamy, "The Infrared Spectra of Complex Molecules", Methuen & Co., Ltd. London, p. 168.
7) L. J. Bellamy, ibid., p. 22.