On the Configurations of α-Aminotricarballylic Acids

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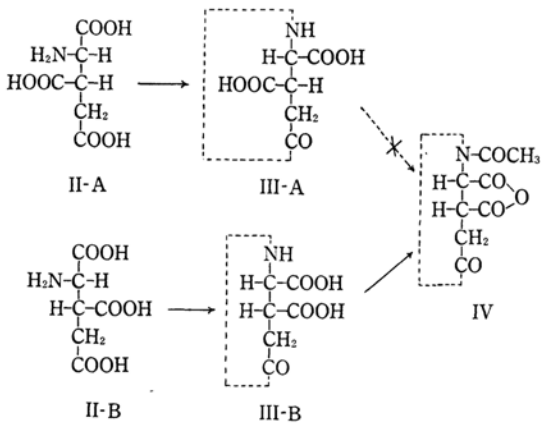
(Received September 10, 1963)

Greenstein et al.[1] have reported on the configuration of the α-asymmetric carbon atoms of α-aminotricarballylic acids and isocitric acids. Recently, the absolute configurations of isocitric acids have been confirmed wholly and undoubtedly by us[2] and by Patterson et al.[3] As a result, the conclusion suggested by Greenstein et al.[1] has been rectified. In this paper, the absolute configurations of α-aminotricarballylic acids will be characterized by confirming the stereostructures of their pyrrolidone derivatives. α-Aminotricarballylic acid (II) was prepared from ethyl acetamidocyanoacetate and diethyl monobromosuccinate by the method of Greenstein et al.,[4] and from diethyl formylsuccinate (I) by Strecker synthesis. The yields of the diastereoisomeric α-aminotricarballylic acids A*2 (II-A) and B*2 (II-B) were obtained at the rate of three to one in the former method, but at the rate of eleven to one in the latter method. The pyrrolidone derivative (III-B) of II-B afforded *N*-acetyl acid anhydride (IV) when heated with acetic anhydride, but from that of II-A (III-A), no acid anhydride was obtained at all. From these results, III-B may be identified as cis, and III-A as trans; therefore, the stereostructures of II-A and II-B may be shown as in the figure. According to Greenstein,[4] (+)- and (−)-alloisocitric lactones were derived from (+)- and (−)-II-A respectively by the action of nitrite, and, similarly, (+)- and (−)-isocitric lactones were derived from)+)- and (−)-II-B. It is evident that the absolute configurations of the β-asymmetric carbon atoms of α-aminotricarballylic acids are identical with those of the correspoding isocitric acids, because there was no effect on the configurations of the β-carbon atoms in the treatment of α-aminotricarballylic acids with nitrite. The determination of the relative configuration between the β- and α-asymmetric carbon atoms of the diastereoisomeric DL-α-aminotricarballylic acids, therefore, is sufficient to clarify the absolute configurations, of the α-asymmetric carbon atoms of the amino acids. Consequently, the absolute configurations of these amino acids II-A and II-B may be shown as in Table I. This table shows that Lutz-Jirgensons' displacement rule[5] is applicable to these amino acids II-A and II-B, and that in the derivations from amino acids II to hydroxy acids III no Walden inversions are observed.



Experimental

Diethyl Formylsuccinate (I).—From diethyl succinate (50 g.) and ethyl formate (30 g.), I (b. p. 92~105°C/3 mmHg: 41~45 g., 70~77%) was prepared by the method described by Wislicenus.[6]

***α*-Aminotricarballylic Acid A (II-A) and Pyrrolidone Carboxylic Acid B (II-B).**—To the addition product prepared from I (60.6 g.) and sodium hydrogen sulfite (37.5 g.), a solution of sodium cyanide (18 g.) in water (145 ml.) was added. Oily cyanohydrine was separated and added to a concentrated aqueous ammonium hydroxide solution (330 ml.). After the mixture had been allowed to react in a pressure bottle for 30 days at room temperature, the reaction mixture was concentrated and the

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1) M. Winitz, S. M. Birnbaum and J. P. Greenstein, *J. Am. Chem. Soc.*, **77**, 716 (1955).

2) T. Kaneko, H. Katsura, H. Asano and K. Wakabayashi, *Chem. & Ind.*, **1960**, 1187; T. Kaneko and H. Katsura, ibid., **1960**, 1188; H. Katsura, *J. Chem. Soc. Japan, Pure Chem. Sec. (Nippon Kagaku Zasshi)*, **82**, 91, 92, 98 (1961).

3) J. P. Glusker, A. L. Patterson, W. E. Lore and M. L. Dornberg, *J. Am. Chem. Soc.*, **80**, 4426 (1958); A. L. Patterson, C. K. Johnson, D. Van der Helm and J. A. Minkin, ibid., **84**, 309 (1962).

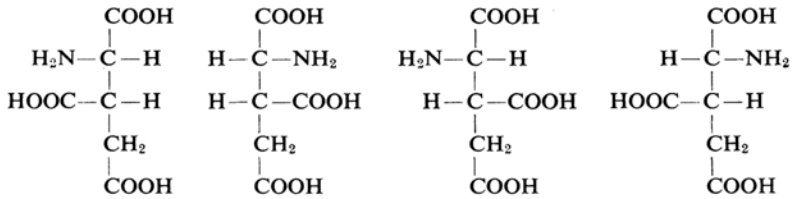
4) J. P. Greenstein, N. Izumiya, M. Winitz and S. M. Birnbaum, ibid., **77**, 707 (1955).

*2 A and B were named by Greenstein.[4]

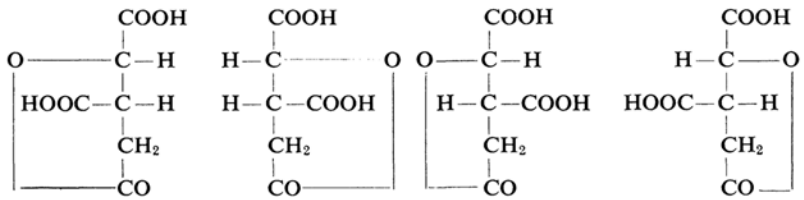
5) O. Lutz and B. Jirgensons, *Ber.*, **63**, 448 (1930); **64**, 1221 (1931); **65**, 784 (1932).

6) W. Wislicenus, E. Boeklen and F. Reute, *Ann.*, **363**, 340 (1908).

TABLE I. THE ABSOLUTE CONFIGURATIONS OF α-AMINOTRICARBALLYLIC ACIDS AND ISOCITRIC ACIDS



		II-A		II-B	
$[\alpha]_D$ in HCl		+36.4°	−36.5°	+48.0°	−48.7°
$[\alpha]_D$ in H_2O		+ 7.5°	− 6.8°	+32.8°	−33.5°
Absolute configuration*	α	S	R	S	R
	β	S	R	R	S



		III-A		III-B	
$[\alpha]_D$ in H_2O		+41.0°	−40.5°	+60.9°	−62.0°
Absolute configuration*	α	S	R	S	R
	β	S	R	R	S

*) This is specified by the (R)-, (S)-system of D. S. Cahn, C. K. Ingold and V. Prelog (*Experientia*, **12**, 81 (1956)).

TABLE II. PAPER CHROMATOGRAM OF α-AMINOTRICARBALLYLIC ACIDS (II-A AND II-B) AND PYRROLIDONE CARBOXYLIC ACIDS (III-A AND III-B)

Solvent	R_f-value			
	II-A	II-B	III-A*	III-B*
n-Butanol : acetic acid : water (4 : 1 : 5(v/v), upper layer)	0.16	0.19	0.45	0.39
Phenol : water : 85% formic acid (3 g. : 1 ml. : 1%)	0.25	0.25	0.59	0.59
Isopropanol : *t*-butanol : benzylalcohol : water : 85% formic acid (1 ml. : 1 ml. : 3 ml. : 1 ml. : 2%)			0.53	0.44
t-Butanol : benzylalcohol : water : 85% formic acid (5 ml. : 15 ml. : 2 ml. : 1%)			0.44	0.36
n-Butanol : benzylalcohol : water : 85% formic acid (5 ml. : 5 ml. : 1 ml. : 1%)			0.40	0.33

* Colored by spraying with brom phenol blue solution

residue was refluxed with 6 N hydrochloric acid (800 ml.) for 7 hr. Inorganic salts were removed by extraction from the hydrolysate with cold ethanol (500 ml.), and chloride ions were removed by the aid of silver carbonate (38 g.); then the solution was treated with hydrogen sulfide. When the purified solution was concentrated and kept at 5°C for 20 hr., II-A (14 g.) deposited as a solid and was recrystallized from water.

Found: C, 37.77; H, 4.99; N, 7.23. Calcd. for $C_6H_9O_6N$: C, 37.70; H, 4.75; N, 7.33%.

Another crop (3 g.) was obtained by the concentration of the above filtrate.

The filtrate separated from II-A crystals was made to pH 5 with an aqueous sodium hydroxide solution, and a solution of copper acetate (65 g.) in hot water (650 ml.) was added to this solution to give blue crystals of copper salt (14 g.), which were collected after standing at room temperature for 20 hr. The copper was removed as copper sulfide, and the solution was refluxed with a large amount of water for 7 hr. When the solution was concentrated and kept at 5°C for 20 hr., III-B (1.5 g.) was obtained and recrystallized from water; m. p. 225°C (decomp.): lit.,[4] m. p. 230°C.

Found: C, 41.29; H, 4.16; N, 8.01. Calcd. for

$C_6H_7O_5N$: C, 41.62; H, 4.08; N, 8.09%.

Pyrrolidone Carboxylic Acid A (III-A).—From II-A (12 g.), III-A (8.5 g.) was obtained by the method described by Greenstein[4] and then recrystallized from water; m. p. 210°C: lit.,[4] 210°C. This sample contains one mole of the water of crystallization.

Found: C, 37.70; H, 4.73; N, 7.42; H_2O, 9.82 (dried at 90~100°C in vacuo for 18 hr.). Calcd. for $C_6H_7O_5N \cdot H_2O$: C, 37.70; H, 4.75; N, 7.33; H_2O, 9.43%.

Acid Anhydride (IV) of *N*-Acetyl-pyrrolidone Carboxylic Acid B.—III-B (2.7 g.) was dissolved in acetic anhydride (400 ml.) by heating it gently over a 30-min. period, and then the solution was heated at 120~140°C for 15 min. After some insoluble materials had been filtered off from the hot reaction mixture, the solution was cooled to room temperature. IV (2.1 g.) thereupon crystallized out, and yet another crop (0.3 g.; total, 2.4 g., 80%) was obtained by the cocentration of the filtrate; m. p. 225°C (decomp.). A sample (1 g.) was recrystallized from acetic anhydride and washed with acetone. The pure substance (0.7 g.) was obtained after drying it over phosphorus oxide in a vacuum desiccator; m. p. 225°C (decomp.).

Found: C, 48.68; H, 3.55; N, 7.11. Calcd. for $C_8H_7O_5N$: C, 48.74; H, 3.58; N, 7.11%.

When this sample (1 g.) was hydrolyzed with 2 N hydrochloric acid (30 ml.), III-B (m. p. 225°C (decomp): 0.4 g.) was recovered.

The R_f values of II-A and II-B, and III-A and III-B are shown in Table II.

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