NOTES

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Studies of the *N*-Oxides of *N*,*N*-Dialkylamino Acids. III. The Syntheses of *N*,*N*-Dimethyl Acidic Amino Acids and Related Compounds

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In the previous papers of this series, the preparations of *N*,*N*-dimethyl neutral amino acid *N*-oxides,[1] and *N*,*N*-dialkylglycine *N*-oxides[2] were investigated. In the present studies, the preparations of *N*,*N*-dimethyl acidic amino acid *N*-oxides have been investigated. The *N*,*N*-dimethylations of acidic amino acids by catalytic reductive condensation with formaldehyde were performed by means of a procedure similar to that reported in the previous papers. The results obtained are summarized in Table 1.

The oxidations of *N*,*N*-dimethyl L- and DL-glutamic acid with a mixture of aqueous hydrogen peroxide and acetic acid gave the corresponding *N*-oxides in good yields after treatment as described in the previous paper. However, in the similar reaction of *N*,*N*-dimethyl-L-aspartic acid, the expected *N*-oxide could not be obtained with a similar treatment, rather, fumaric acid, the decomposition product of the corresponding *N*-oxide, was obtained in an almost pure state in a good yield. This type of decomposition is well-known as "Cope elimination".[3] Unfortunately, all attempts to obtain the corresponding *N*-oxide in the pure state were unsuccessful. The results obtained are summarized in Table 2.

When water was used instead of aqueous hydrogen peroxide in the above reaction, no reaction occurred under the same reaction conditions and the unchanged starting material was recovered.

TABLE 1. *N*,*N*-DIMETHYL ACIDIC AMINO ACIDS

Parent amino acid	Reduction period (50°C)	Yield (%)	Mp (°C)	R_f Value[a]	C%		H%		N%	
					Found	Calcd	Found	Calcd	Found	Calcd
L-Asp	7 hr	88	198	0.27	44.57	44.71	6.74	6.88	8.63	8.69
DL-Asp	7	89	195	—	44.74	44.71	6.84	6.88	8.68	8.69
L-Glu	6	89	196	0.36	47.87	47.99	7.56	7.48	7.84	8.00
DL-Glu	6	90	199	—	47.94	47.99	7.45	7.48	8.02	8.00

a) A 1-butanol-acetic acid-water (60:15:25) solvent system was used. The location of the paper chromatogram was detected by spraying 50% aqueous ethanol solution of bromophenol blue.

TABLE 2. OXIDATION PRODUCT OF *N*,*N*-DIMETHYL ACIDIC AMINO ACIDS

Starting amino acid	Oxidation period (60°C)	Yield of product (%)	Mp (dec.) (°C)	R_f Value[a]	C%		H%		N%		ν_{N-O} cm^{-1}
					Found	Calcd	Found	Calcd	Found	Calcd	
L-Asp	7 hr	72[b]	—	0.81[c]	41.73	41.39	3.47	3.47	—	—	—
L-Glu	8	87	163	0.49	43.98	43.97	6.85	6.85	7.36	7.33	971
DL-Glu	8	89	160	—	44.20	43.97	6.84	6.85	7.06	7.33	970

a) The same procedure was used as described in Table 1.
b) This is yield of fumaric acid. c) This vlaue is that of fumaric acid.

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[1] Y. Ikutani, This Bulletin, **41**, 1679 (1968).

[2] Y. Ikutani, *ibid.*, **42**, 2330 (1969).

[3] A. C. Cope and E. R. Trumbull, "Organic Reactions," Vol. 11, Chap. 5 (1960).

However, on prolonged heating at an elevated temperature, deamination occurred to afford dimethylammonium hydrogen fumarate.

A similar reaction partially occurred in the aqueous solution of *N*,*N*-dimethyl-L-aspartic acid, and dimethylammonium hydrogen fumarate and *N*,*N*-dimethyl-DL-aspartic acid were thus obtained in 42 and 40% yields respectively. *N*,*N*-Dimethyl-L-glutamic acid was not decomposed under similar conditions, but a complete racemization occurred.

Experimental

***N*,*N*-Dimethyl-L-glutamic Acid.** A mixture of 15 g of L-glutamic acid, 1.5 g of a silk-palladium catalyst, 50 m*l* of 37% aqueous formaldehyde, and 150 m*l* of water was shaken in an autoclave at 50—55°C for 6 hr. The catalyst was then removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. A small amount of paraformaldehyde was present in the product; it was removed by re-evaporation with water. The resulting solid was crude *N*,*N*-dimethyl-L-glutamic acid. It was collected, washed with acetone several times, and dried. The crude product was dissolved in a minimum volume of hot 50% aqueous ethanol, decolorized with a small amount of charcoal, and filtered. About the same volume of acetone was then added in small portions, and the mixture was stored in a refrigerator overnight. Fine crystals of *N*,*N*-dimethyl-L-glutamic acid were collected by filtration, washed with acetone, and dried under reduced pressure. The yield was 15.5 g (89%).

***N*,*N*-Dimethyl-L-glutamic Acid *N*-Oxide.** A mixture of 4.0 g of *N*,*N*-dimethyl-L-glutamic acid, 20 m*l* of 30% aqueous hydrogen peroxide, and 40 m*l* of acetic acid was warmed at 60°C for 8 hr. To the reaction mixture, about 50 m*l* of water was then added, after which the mixture was concentrated to about a half volume under reduced pressure while being gently warmed below 40°C. After this procedure had been repeated until the distillate gave a negative reaction to a potassium iodide starch test, the solution was evaporated to dryness under reduced pressure. The crude products were collected by filtration with a small amount of acetone, washed with acetone, and dried under reduced pressure. The crude *N*,*N*-dimethyl-L-glutamic acid *N*-oxide thus obtained was dissolved in a minimum volume of hot water, decolorized with a small amount of charcoal, and filtered. About the same volume of acetone was then added in small portions, and the mixture was stored in a refrigerator overnight. Fine crystals were then collected by filtration, washed with acetone, and dried under reduced pressure. The yield was 4.0 g (87%).

The Oxidation of *N*,*N*-Dimethyl-L-aspartic Acid. A mixture of 4.0 g of *N*,*N*-dimethyl-L-aspartic acid, 20 m*l* of 30% aqueous hydrogen peroxide, and 40 m*l* of acetic acid was warmed at 60°C for 7 hr. The reaction product was then treated in a manner similar to that in the experiment described in the case of *N*,*N*-dimethyl-L-glutamic acid. The residue thus obtained was fumaric acid in an almost pure state; it was collected by filtration with a small amount of cold water. The yield was 2.1 g (72%). (Found: C, 41.73; H, 3.47%.)

The Decomposition of *N*,*N*-Dimethyl-L-aspartic Acid with Aqueous Acetic Acid. A mixture of 4.0 g of *N*,*N*-dimethyl-L-aspartic acid, 20 m*l* of water, and 40 m*l* of acetic acid was heated on a boiling water bath for 24 hr. The residual solution was then dried up under reduced pressure. The residual syrup was dissolved in a small volume of water, and the solution was dried up under reduced pressure. This procedure was repeated twice; the residue was then solidified, collected by filtration with a small amount of acetone, and dried under reduced pressure. This substance was identified as dimethylammonium hydrogen fumarate by a comparison with an authentic sample prepared from equimolar fumaric acid and dimethylamine. The yield was 3.3 g (83%). (Found: C, 44.43; H, 6.82; N, 8.81%.)

The Decomposition and Racemization of *N*,*N*-Dimethyl-L-aspartic Acid in an Aqueous Solution. A solution of 5.0 g of *N*,*N*-dimethyl-L-aspartic acid in 100 m*l* of water was heated on a boiling water bath for 24 hr. The residual solution was then evaporated to dryness under reduced pressure. The residue was suspended in a small volume of ethanol, and the suspension was dried up under reduced pressure to remove a trace of water. This procedure was repeated twice; then the residue was collected by filtration with a small amount of acetone, washed with acetone, and dried under reduced pressure. The residue was extracted with a small amount of hot ethanol several times; *N*,*N*-dimethyl-DL-aspartic acid was thus separated as precipitates from the mixture because of its insolubility. The yield was 2.0 g (40%). (Found: C, 44.74; H, 6.84; N, 8.68%.) The extract was dried up under reduced pressure; 2.1 g (42%) of dimethylammonium hydrogen fumarate were thus obtained.

The Racemization of *N*,*N*-Dimethyl-L-glutamic Acid. A mixture of 4.0 g of *N*,*N*-dimethyl-L-glutamic acid, 20 m*l* of water, and 40 m*l* of acetic acid was heated on a boiling water bath for 20 hr. The residual solution was then treated in a manner similar to that used in the experiment described in the case of *N*,*N*-dimethyl-L-aspartic acid, The product thus obtained was *N*,*N*-dimethyl-DL-glutamic acid, weighing 3.8 g (95%). (Found: C, 47.87; H, 7.58; N, 8.10%).

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