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Studies of the *N*-Oxides of *N*,*N*-Dialkylamino Acids. I. The Syntheses of *N*,*N*-Dimethyl Neutral Amino Acids and Corresponding *N*-Oxides

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The *N*,*N*-dimethyl derivatives of neutral amino acids, such as glycine, L-alanine, DL-alanine, L-valine, DL-valine, L-leucine, L-phenylalanine, and L-tyrosine, were prepared by the catalytic reductive condensation of the corresponding amino acids with formaldehyde. The *N*-oxides were satisfactorily synthesized by the oxidation of the *N*,*N*-dimethyl derivatives with an aqueous mixture of hydrogen peroxide and acetic acid. The reaction conditions, the analytical data, and some properties of the products are presented.

As a part of an investigation of the syntheses and reactions of *N*,*N*-dialkylamino acids, the syntheses of *N*,*N*-dimethyl neutral amino acids and the corresponding *N*-oxides have been studied. Although several reagents, such as methyl iodide, dimethyl sulfate, and diazomethane, are available for the alkylation of the amino group, the most suitable method is the catalytic reductive condensation of amino acid with aldehyde.[1,2] In an earlier paper, Sweely and Horning reported the synthesis and ferric ion - catalyzed reactions of *N*,*N*-dimethylglycine *N*-oxide.[3] However, the melting point of the substance was indistinct, and the results of elementary analysis were not identical with the calculated value. The present author has prepared the various *N*, *N*-dimethyl neutral amino acids in good yields and has oxidised them to the corresponding *N*-oxides satisfactorily. The *N*, *N*-dimethylations were carried out at 50°C by the catalytic reductive condensation of an aqueous solution of neutral amino acid and formaldehyde in the presence of a silk-palladium catalyst, which showed no reductivity in responce to any aldehyde.[4] The period of the reduction depends on the solubility of the parent amino acid; for example, the *N*,*N*-dimethylation of L-tyrosine in an aqueous suspension proceeded very slowly. The reaction product was a mixture consisting of the *N*, *N*-dimethyl derivative and a trace of the unchanged parent amino acid. The *N*-monomethyl derivative has not been obtained in any case. The analytical data and some properties of the *N*, *N*-dimethyl derivatives are summarized in Table 1.

Generally the oxidation of aliphatic tertiary amine with aqueous hydrogen peroxide gives the corresponding *N*-oxide. However, in the case of *N*,*N*-dimethylamino acid, no reaction occurred at either room temperature or 60°C and the starting substance was recovered unchanged. Sweely and Horning prepared *N*,*N*-dimethylglycine *N*-oxide by the oxidation of *N*,*N*-dimethylglycine in an aqueous mixture of hydrogen peroxide and barium hydroxide. The present author oxidized the *N*,*N*-dimethylamino acids to the corresponding *N*-oxides using an aqueous mixture of hydrogen peroxide and acetic acid at 60°C. The most suitable oxidation conditions were detected by paper chromatographic studies of the reaction mixture. After the oxidation, the same volume of water was added to the reaction mixture and the solution was concentrated carefully below 40°C under reduced pressure. After this procedure had been repeated until the distillate gave a negative reaction in a potassium iodide starch test, the residue was dried up under reduced pressure. When the crude *N*-oxides were recrystallized from ethanol-acetone, the *N*-oxides obtained were of a high purity.

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[1] R. E. Bowman and H. H. Stroud, *J. Chem. Soc.*, **1950**, 1342.

[2] K. Kanao, *Yakugaku Zasshi* (*J. Pharm. Soc. Japan*), **66**, 4 (1946).

[3] C. C. Sweely and E. C. Horning, *J. Am. Chem. Soc.*, **79**, 2620 (1957).

[4] Y. Izumi, This Bulletin, **32**, 932 (1959).

Table 1. *N*, *N*-dimethyl neutral amino acids

Parent amino acid	Reduction period (50°C) (hr)	Yield (%)	Mp (°C)	R_f Value[a]	C %		H %		N %	
					Found	Calcd	Found	Calcd	Found	Calcd
Gly	8	84	179	0.33	46.76	46.59	8.89	8.80	13.56	13.58
L-Ala	6	81	183	0.36	51.27	51.26	9.50	9.46	11.94	11.96
DL-Ala	7	92	182	0.36	51.18	51.26	9.45	9.46	12.02	11.96
L-Val	8.5	92	153	0.59	57.51	57.90	10.29	10.41	9.84	9.65
DL-Val	10	85	151	0.59	58.40	57.90	10.38	10.41	9.84	9.65
L-Leu	15	84	197	0.69	60.29	60.34	10.63	10.76	8.74	8.80
L-Phe	5	96	222	0.67	68.08	68.37	7.83	7.82	7.24	7.25
L-Tyr[b]	22	83	273	0.52	62.64	63.14	7.20	7.23	6.89	6.69
L-Tyr[c]	22	83	274	0.52	62.96	63.14	7.19	7.23	6.86	6.69

a) A *n*-butanol - acetic acid - water (60 : 15 : 25) solvent system was used. The location of the paper-chromatogram was carried out by spraying of alkaline aqueous ethanol solution of thymol blue.

b) This substance was obtained as filamentous needles.

c) This substance was obtained as short prisms.

Table 2. *N*, *N*-dimethyl neutral amino acid *N*-oxides

Starting amino acid	Oxidation time (60°C) (hr)	Yield (%)	Mp (dec.) (°C)	R_f Value[a]	C %		H %		N %		ν_{N-O} cm^{-1}
					Found	Calcd	Found	Calcd	Found	Cacld	
Gly	7	83	136	0.44	40.70	40.33	7.72	7.62	11.84	11.76	972
L-Ala	6	74	120	0.50	45.22	45.10	8.25	8.33	10.40	10.52	963
L-Val	7	91	103	0.76	52.23	52.15	9.49	9.38	8.59	8.69	968
L-Leu	7	98	114	0.86	54.91	54.83	9.70	9.78	7.77	7.99	980
L-Phe	6	80	139	0.77	63.27	63.14	7.36	7.23	6.54	6.69	976
L-Tyr[b]	3	60	163	0.62	54.10	54.31	7.01	7.04	5.74	5.76	966
L-Tyr[c]	—	—	—	—	58.66	58.65	6.59	6.71	6.09	6.22	—

a) Same procedure was used as described in Table 1.

b) This substance was obtained as monohydrated crystal.

c) This substance was anhydrous powder.

N,*N*-Dimethyl-L-tyrosine *N*-oxide crystallized as monohydrate, and the crystal water was removed at 80°C under reduced pressure over an 8-hr period. The *N*-oxides show the infrared absorption band in the 960—980 cm^{-1} region, as does ordinary aliphatic tertiary amine *N*-oxide.[5] The basicity of the *N*-oxides are weaker than those of the corresponding *N*,*N*-dimethyl derivatives. The elementary analyses and some properties of the *N*-oxides are summarized in Table 2. The *N*-oxides were easily reduced to the parent *N*,*N*-dimethylamino acids by catalytic reduction.

Experimental

***N*,*N*-Dimethylglycine.** A mixture of 19 g of glycine, 1.5 g of a silk-palladium catalyst, 80 m*l* of 37% aqueous formaldehyde, and 120 m*l* of water was placed in an autoclave, which was then filled with hydrogen. The mixture was shaken at 50°C for 7 hr, by which time the theroretical amount of hydrogen had been taken up. The catalyst was then filtered off, and the filtrate was evaporated under reduced pressure. A small amount of paraformaldehyde was present in the product; it was removed by re-evaporation with water. The residual syrup was dissolved in a small volume of ethanol, and the solution was dried up to remove a trace of water. After this procedure had been repeated three times, the crystalline product appeared. About 50 m*l* of acetone was added in small portions to the precipitates, and the crystallization was complete. The resulting crystalline precipitates were collected by filtration, washed with acetone several times, and then dried under reduced pressure. The yield of the crude product was almost equal to the theoretical yield. The crude product was dissolved in a minimum volume of hot ethanol, decolorized with a small amount of charcoal, and filtered. About 150 m*l* of acetone were 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 21.7 g (83%). This substance was very hygroscopic and deliquescent, and was soluble in ethanol and almost insoluble in acetone.

Other *N*,*N*-Dimethyl Derivatives of Neutral Amino Acids. *N*,*N*-Dimethyl derivatives of all the other neutral amino acids except L-tyrosine were

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[5] R. Mathis-Noel, R. Wolf and F. Gallais, *Compt. rend.*, **242**, 1873 (1956).

obtained by a similar method. *N*,*N*-Dimethyl-L-alanine and *N*,*N*-dimethyl-DL-alanine were very hygroscopic and deliquescent prisms. *N*,*N*-Dimethyl-L-valine and *N*,*N*-dimethyl-DL-valine were slightly hygroscopic. *N*,*N*-Dimethyl-L-leucine and *N*,*N*-dimethyl-L-phenylalanine were not hygroscopic. The *N*,*N*-dimethylation of 6.2 g of L-tyrosine in 20 m*l*-tyrosine 20 m*l* of 37% aqueous formaldehyde and 230 m*l* of water proceeded very slowly for about 22 hr. By a treatment similar to that described above, a crude product was obtained. The crude product was dissolved in a minimum volume of hot water, decolorized with charcoal, and filtered. To the filtrate, 50 m*l* of acetone were added, and the resulting mixture was rapidly cooled in a refrigerator. Fine filamentous needles were then collected by filtration, washed with acetone, and dried under reduced pressure. The yield was 6.0 g (83%). In another recrystallization, when a hot, saturated aqueous solution was allowed to cool slowly, short prisms were obtained. They showed almost the same properties, except that slight differences were observed in the infrared absorption spectra.

***N*,*N*-Dimethylglycine *N*-Oxide.** A solution of 4 g of *N*,*N*-dimethylglycine, 20 m*l* of 30% aqueous hydrogen peroxide, and 40 m*l* of acetic acid was warmed at 60°C for 7 hr. To a reaction mixture, about 50 m*l* of water were added, after which the mixture was concentrated to about a half volume while being gently warmed below 40°C under reduced pressure. 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 residual syrup was dissolved in a small volume of ethanol, and the solution was dried up under reduced pressure. This procedure was repeated twice, after which the residue was crystallized. The crude products were collected with acetone, washed with acetone, and dried under reduced pressure. The product thus obtained was recrystallized by a method similar to that described above. The yield of dimethylglycine *N*-oxide was 3.8 g (83%).

Other *N*,*N*-Dimethyl Neutral Amino Acid *N*-Oxides. The *N*-oxides of *N*,*N*-dimethyl-L-alanine, *N*,*N*-dimethyl-DL-alanine, *N*,*N*-dimethyl-L-valine, *N*,*N*-dimethyl-DL-valine, *N*,*N*-dimethyl-L-leucine, and *N*,*N*-dimethyl-L-phenylalanine were obtained in the same manner. However, *N*,*N*-dimethyl-L-tyrosine *N*-oxide was obtained as monohydrated crystals and the water was removed by heating at 80°C for 8 hr under reduced pressure.

The Reduction of *N*,*N*-Dimethylglycine *N*-Oxide to *N*,*N*-Dimethylglycine. A mixture of 2.4 g of *N*,*N*-dimethylglycine *N*-oxide, 1.5 g of a silk-palladium catalyst, and 150 m*l* of water was placed in an autoclave with hydrogen. The mixture was shaken at 40°C for 30 min. When the reaction mixture was then treated in the manner described above, 1.7 g of a product was obtained. The melting point of this sample was not depressed by admixture with authentic *N*,*N*-dimethylglycine, and the two substances had completely identical infrared absorption spectra. The recovery of *N*,*N*-dimethylglycine was 1.6 g (80%).

Found: C, 46.48; H, 8.98; N, 13.49%. Calcd for $C_4H_9O_2N$: C, 46.59; H, 8.80; N, 13.58%.

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