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Studies of the *N*-Oxides of *N,N*-Dialkylamino Acids. II. The Syntheses of *N,N*-Dialkylglycine and Corresponding *N*-Oxides

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The reductive condensations of glycine with various aliphatic straight-chain aldehydes, such as acetaldehyde, propionaldehyde, and *n*-butyraldehyde, give the corresponding *N,N*-dialkyl derivatives. The *N*-monoalkyl derivative has not been obtained in any case. In another type of reactions, those with aliphatic branched-chain aldehydes, such as isobutyraldehyde and isovaleraldehyde, considerable *N*-monoalkylation takes place besides the dialkylation. The oxidations of *N,N*-dialkylglycine to the corresponding *N*-oxides have been successfully performed using an aqueous mixture of hydrogen peroxide and acetic acid except in the case of *N,N*-diisobutylglycine. Similar reductive condensations of sarcosine with various aliphatic aldehydes, such as acetaldehyde, propionaldehyde, *n*- and iso-butyraldehyde, and isovaleraldehyde, gave the corresponding *N*-alkylsarcosines. *N*-Isobutyl and *N*-isoamyl sarcosine were also obtained by the methylation of the corresponding *N*-monoalkylglycine. The *N*-oxides of *N*-alkylsarcosine were synthesized by a procedure similar to that described above.

In the preceding paper of this series,[1] the *N,N*-dimethylations of various neutral amino acids, such as glycine, L-alanine, DL-alanine, L-valine, DL-valine, L-leucine, L-phenylalanine, and L-tyrosine, and the oxidations to the corresponding *N*-oxides were investigated. In the present study, the preparations of *N,N*-dialkylglycine *N*-oxides have been studied. The alkylations of glycine by the catalytic reductive condensation with various aliphatic aldehydes were performed by a procedure similar to that reported in the preceding paper. The results obtained are summarized in Table 1.

These results clearly indicate that the corresponding *N,N*-dialkyl derivatives were obtained as the alkylation products when aliphatic straight-chain aldehydes were employed in these reactions. The *N*-monoalkyl derivatives initially formed seem to be more reactive to the carbonyl group of the aldehydes and readily react with an excess of aldehydes to give the corresponding *N,N*-dialkyl derivatives.

On the other hand, in the case of the reductive alkylation of glycine with aliphatic branched-chain aldehydes, such as isobutyraldehyde and isovaleraldehyde, considerable monoalkylation took place besides the dialkylation. However, when an excess of the aldehyde was used, the *N,N*-dialkyl derivative was obtained in a nearly quantitative yield. These results show the bulkiness of the substituent of aliphatic branched-chain aldehydes considerably inhibits the condensation reaction of the *N*-monoalkyl glycine initially formed and the aldehyde. This assumption is supported by the fact that the *N,N*-dialkylation of glycine with isovaleraldehyde proceeds more rapidly than that of the similar reaction with isobutyraldehyde. The analytical data and some properties of *N,N*-dialkylglycine are summarized in Table 2.

The oxidations of *N,N*-dialkyl derivatives of glycine to the corresponding *N*-oxides were performed successfully by the method described in the preceding paper. However, in the case of *N,N*-diisobutylglycine, all attempts to obtain the corresponding *N*-oxide were unsuccessful and the unchanged *N,N*-diisobutylglycine was recovered. This unfavorable result is probably brought about by the steric hindrance of the bulky isobutyl residue. The analytical data and some properties of the *N*-oxides of *N,N*-dialkylglycine are summarized in Table 3.

Similar reductive condensations of sarcosine with various aliphatic aldehydes, such as acetaldehyde, propionaldehyde, *n*- and iso-butyraldehyde, and isovaleraldehyde, gave the corresponding

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

N-alkylsarcosines. These analytical data and some properties are summarized in Table 4.

N-Isobutyl and *N*-isoamyl sarcosine were also synthesized by the reductive methylation of the corresponding *N*-monoalkylglycine with formaldehyde.

The oxidations of *N*-alkylsarcosine to the *N*-oxides were performed by a procedure similar to

Table 1. The catalytic reductive condensation of glycine with various aliphatic aldehydes

Aldehyde	Molar ratio (aldehyde/glycine)	Reaction conditions		Recovery of glycine (%)	Yield of the product (%)	
		Temp. (°C)	Time (hr)		Monoalkyl	Dialkyl
Acetaldehyde	2	40—45	4	6	none	85
Propionaldehyde	2	40—45	4	13	none	80
n-Butylaldehyde	1	45—50	5	46	trace	41
	2	45—50	6	11	none	83
Isobutyraldehyde	1	50—55	4	65	23	7
	1.5	50—55	7	36	40	20
	2	50—55	9	22	40	36
Isovaleraldehyde	1	50—55	3	32	38	25
	2	50—55	6	16	19	59

Table 2. *N*, *N*-Dialkylglycine

Alkyl group	Mp (°C)	R_f Value*	Formula	C, %		H, %		N, %	
				Found	Calcd	Found	Calcd	Found	Calcd
Ethyl	123	0.65	$C_6H_{13}O_2N$	55.00	54.94	9.92	9.99	10.59	10.68
n-Propyl	129	0.68	$C_8H_{17}O_2N$	60.22	60.34	10.81	10.76	8.80	8.80
n-Butyl	135	0.83	$C_{10}H_{21}O_2N$	64.01	64.13	11.24	11.30	7.30	7.48
Isobutyl	98	0.76	$C_{10}H_{21}O_2N$	64.49	64.13	11.23	11.30	7.44	7.48
Isoamyl	172	0.88	$C_{12}H_{25}O_2N$	67.10	66.93	11.81	11.70	6.35	6.51

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

Table 3. *N*, *N*-Dialkylglycine *N*-oxide

Alkyl group	Yield (%)	Mp (dec. °C)	R_f Value	C, %		H, %		N, %		ν_{N-O} cm^{-1}
				Found	Calcd	Found	Calcd	Found	Calcd	
Ethyl	70	110	0.76	48.69	48.96	8.95	8.90	9.41	9.52	999
n-Propyl	87	93	0.81	54.81	54.83	9.80	9.78	7.94	7.99	987
n-Butyl	90	92	0.87	58.99	59.08	10.41	10.41	6.94	6.89	975
Isoamyl	92	148	0.93	62.15	62.30	10.83	10.89	5.97	6.05	1010

Table 4. *N*-Alkylsarcosine

Alkyl group	Yield (%)	Mp (°C)	R_f Value	C, %		H, %		N, %	
				Found	Calcd	Found	Calcd	Found	Calcd
n-Propyl	83	113	0.53	54.99	54.94	10.09	9.99	10.66	10.68
n-Butyl	87	95	0.66	58.09	57.90	10.44	10.41	9.42	9.65
Isobutyl (from sarcosine)	93	111	0.64	57.68	57.90	10.48	10.41	9.48	9.65
Isobutyl (from glycine *via* *N*-isobutyl glycine)	—	110	—	58.12	57.90	10.37	10.41	9.41	9.65
Isoamyl (from sarcosine)	87	132	0.71	60.13	60.34	11.02	10.76	8.65	8.80
Isoamyl (from glycine *via* *N*-isoamyl glycine)	—	136	—	60.50	60.34	10.84	10.76	8.65	8.80

TABLE 5. *N*-ALKYSARCOSINE *N*-OXIDE

Alkyl group	Yield (%)	Mp (°C)	R_f Value	C, % Found	C, % Calcd	H, % Found	H, % Calcd	N, % Found	N, % Calcd	ν_{N-O} cm^{-1}
n-Propyl	63	91	0.64	49.57	48.96	9.30	8.90	9.50	9.52	997
n-Butyl	67	98	0.78	52.01	52.15	9.41	9.38	8.89	8.69	985
Isobutyl (from sarcosine)	71	137 (dec.)	0.74	52.38	52.15	9.41	9.38	8.67	8.69	952
Isobutyl (from glycine *via* *N*-isobutyl glycine)	—	135 (dec.)	—	52.24	52.15	9.47	9.38	8.62	8.69	—
Isoamyl (from sarcosine)	65	130	0.79	54.80	54.83	9.58	9.78	7.78	7.99	994
Isoamyl (from glycine *via* *N*-isoamyl glycine)	—	127	—	54.54	54.83	9.75	9.78	7.73	7.99	—

that described in the preceding paper. The analytical data and some properties of *N*-alkylsarcosine *N*-oxides are summarized in Table 5. The optical resolutions of *N*-alkylsarcosine *N*-oxides are currently under investigation, the results will be reported in detail elsewhere.

Experimental

The Dialkylation of Glycine with Various Aliphatic Straight-chain Aldehydes. The *N,N*-dialkyl derivatives of glycine were obtained by the catalytic reductive condensation of glycine with various aliphatic straight-chain aldehydes, such as acetaldehyde, propionaldehyde, and *n*-butyraldehyde, according to a procedure smilar to that described in the preceding paper.

The Alkylation of Glycine with Aliphatic Branched-chain Aldehydes. A mixture of 15 g of glycine, 1.5 g of the silk-palladium catalyst, 29 g of isobutyraldehyde, 100 m*l* of ethanol, and 130 m*l* of water was shaken with hydrogen in an autoclave at 50—55°C for 9 hr. The catalyst was then removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The residue was suspended to a small volume of ethanol, and the suspension was dried up under reduced pressure to remove a trace of water. The residue was then extracted with two 50 m*l* portions of hot ethanol to dissolve the *N*-isobutyl and *N,N*-diisobutyl glycine. Unreacted glycine was removed as a precipitate. The combined extract was dried up under reduced pressure. The residue was then re-extracted with two 50 m*l* portions of hot acetone to dissolve *N,N*-diisobutyl glycine, while *N*-isobutylglycine remained as a precipitate. The yield of crude *N*-isobutylglycine was 10.5 g. The pure substance was obtained by the recrystallization of the crude product from hot ethanol, it melted at 207°C with decomposition.

Found: C, 54.52; H, 9.95; N, 10.71%. Calcd for $C_6H_{13}O_2N$: C, 54.94; H, 9.99; N, 10.68%.

When the extracted filtrate was dried up under reduced pressure, 13.5 g of crude *N,N*-diisobutylglycine was obtained. The product was dissolved in a minimum volume of a hot mixture of acetone and isopropyl ether (1 : 1), decolorized with a small amount of charcoal, and filtered. About the same volume of isopropyl ether was then added in small portions, and the mixture was stored in a refrigerator overnight. Fine crystals of *N,N*-diisobutylglycine were then collected by filtration, washed with a small amount of isopropyl ether, and dried under reduced pressure.

The reductive alkylation of glycine with isovaleraldehyde was performed in the same manner. The dialkyl derivative was extracted using three 100 m*l* portions of a hot mixture of acetone and ethanol (9 : 1). The *N*-isoamylglycine melted at 235°C with decomposition.

Found: C, 58.12; H, 10.37; N, 9.41%. Calcd for $C_7H_{15}O_2N$: C, 57.90; H, 10.41; N, 9.65%.

***N,N*-Dialkylglycine *N*-Oxides.** These substances were prepared by the oxidation of the corresponding *N,N*-dialkylglycine with an aqueous mixture of hydrogen peroxide and acetic acid according to a procedure similar to that described in the preceding paper except in the case of *N,N*-diisobutylglycine.

***N*-Alkylsarcosine.** The *N*-alkylsarcosines were obtained by the catalytic reductive condensation of sarcosine with the corresponding aliphatic aldehyde. For example, a mixture of 15 g of sarcosine, 1.5 g of the silk-palladium catalyst, 12 g of propionaldehyde, and 150 m*l* of water was shaken with hydrogen in an autoclave at 45—50°C for 6 hr. The catalyst was then removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The residue 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 residual syrup was stored in a desiccator for a week. The crude *N*-*n*-propylsarcosine thus crystallized was filtered with a small amount of isopropyl ether and recrystallized from a hot mixture of acetone and isopropyl ether. Other *N*-alkyl derivatives of sarcosine were obtained by a similar procedure.

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