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Synthetic Studies of Amino Acids by the Use of Copper(II) Complexes. V.[1] The Preparation of Hydroxy Amino Acids by a Set of Improved Procedures

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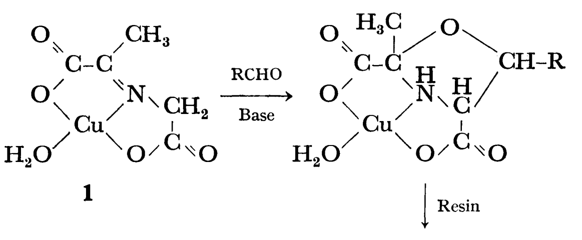
Synopsis. A variety of hydroxy amino acids were prepared by a brief treatment of a resulting mixture, which was obtained by a base-catalyzed condensation reaction of *N*-pyruvylideneglycinatoaquocopper(II) with aldehydes, on a column of Amberlite IR-120B (H form) resin.

The base-catalyzed condensation reaction of *N*-pyruvylideneglycinatoaquocopper(II) (**1**) with aldehydes has been shown[2c,d] to be especially useful in the preparation of 2-amino-2-deoxyaldonic acids from aldehydo sugar derivatives, in contrast with the reaction of bisglycinatocopper(II) *etc.* And it has recently been confirmed that glycine can be isolated from some of the corresponding copper(II) complexes in fairly good yields merely by treating the solution of the complexes on a column of Amberlite IR-120B (H form), even in the case of the solution in aqueous DMF.[1] In order to establish a more effective and facile method of preparing hydroxy amino acids, the present authors undertook an investigation of the preparation of hydroxy amino acids by a set of improved procedures—*i.e.*, the base-catalyzed condensation reaction of **1** with aldehydes[2] and the facile isolating procedure of amino acids.[1]



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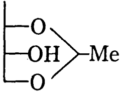
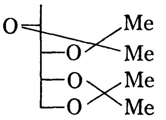
R-CH(OH)-CH(NH_2)-COOH

Base-catalyzed condensation reactions of **1** with acetaldehyde (**2**), propionaldehyde (**3**), *n*-butyraldehyde (**4**), benzaldehyde (**5**), 2,4-*O*-ethylidene-*al*-D-erythrose (**6**), and 2,3;4,5-di-*O*-isopropylidene-*al*-D-arabinose (**7**) were carried out. Each resulting reaction mixture was then divided into two aliquots for the subsequent treatment after adjusting the pH to 4.5 with an aqueous acetic acid solution; one was directly adsorbed on a column of IR-120B (H form), followed by elution with an aqueous ammoniacal solution after washing with water (A procedure); while the other was treated on a column of the ion-exchange resin after the removal of the copper(II) ion by treating it with hydrogen sulfide gas, as has been done traditionally (B procedure), for comparison with the A procedure. The reaction conditions and yields of the corresponding hydroxy amino acids obtained by both A and B procedures are summarized in Table 1. It is possible to discuss the comparative merits of the two procedures directly on the basis of these results because their samples came from the same source. The expected superiority of the A procedure to the B procedure is apparently exhibited in the cases of **2**, **3**, and **6**, which were found to give the corresponding hydroxy amino acid copper(II) complexes easily soluble in water; however, the yields of hydroxy amino acids were not so much improved in the cases of **4**, **5**, and **7**, which were found

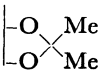
Table 1. An examination of the comparative merit of A and B procedure[a)]

Run	Aldehydes (R–CHO)	R–CHO/**1**	Reaction period (min)	Yields (%) of the corresponding hydroxy amino acids obtained by	
				A procedure[b)]	B procedure[c)]
1	Me– (**2**)[d)]	1.5	120	87.6	71.7
2	Et– (**3**)[e)]	3.0	240	90.1	70.0
3	*n*-Pr– (**4**)[e)]	3.0	240	60.8	57.7
4	Ph– (**5**)[e)]	3.0	540	61.2	65.5
5	 (**6**)[d)]	1.1	45	79.7[f)]	52.1[f)]
6	 (**7**)[d)]	1.1	90	40.1[f)]	34.0[f)]

a) All the reactions were carried out by the use of **1** (5.200 g, 20 mmol) and divided into two aliquots after the treatments as described in d and e. b) The one aliquot was directly adsorbed on a column (3×9 cm) of Amberlite IR-120B (H form), and the column was eluted with 0.5 M aqueous ammoniacal solution (2000 ml) after washing with distilled water (5000 ml). c) The other aliquot was treated with hydrogen sulfide gas, and was successively treated on the column of the ion exchange resin as described in b after the filtration of the resulting copper sufide through the filter-cell. d) The condensation reaction was carried out in an aqueous solution (distilled water: 100 ml) at pH 9.5—9.8 at room temperature, and the resulting mixture was then acidified with 5 M aqueous acetic acid (pH 4.5). The procedure of d and b is termed as A-1 procedure. e) The condensation reaction was carried out in a mixture of methanol (60 ml) and 1 M methanolic sodium methoxide solution (14 ml) at room temperature under nitrogen atmosphere. To the resultant mixture, was added 5 ml of a 5 M aqueous acetic acid solution, and the mixture was diluted with distilled water to a volume of 200 ml. The procedure of e and b is termed as A-2 procedure. f) These products were isolated as the corresponding deblocked derivatives.

to give the corresponding copper(II) complexes less soluble in water. This defficiency in the procedure in the latter cases was, as will be described later, overcome by carrying out treatment with the ion-exchange resin batchwise or by the use of aqueous *N*,*N*-dimethylformamide as the solvent for the condensation reaction and/or as a dissolution-assisting agent prior to treatment on the column of the resin. Consequently, it can be expected that a variety of hydroxy amino acids can be effectively prepared by this set of improved procedures and that, in addition, the copper(II) ion can be recovered by a subsequent washing of the column with an appropriate eluent.

TABLE 2. PREPARATIONS OF HYDROXY AMINO ACIDS BY THE TREATMENT OF A PROCEDURE[a]

Run	Aldehydes (R–CHO)	R–CHO/**1**	Solvent systems	Reaction period (hr)	Yields of hydroxy amino acids obtained by the A procedure (%)[b]
1	Me– (**2**)	1.5	A-1 (pH 9.8)	3.0	87.6 (61[2c])
2	Et– (**3**)	3.0	A-2	4.0	90.1 (77[2c])
3	*n*-Pr– (**4**)	3.0	A-2	4.0	81.2 (75[2c])
4	**4**	3.0	A-6	2.0	84.4
5	*i*-Pr–	3.0	A-2	7.0	73.3 (75[2c])
6	*i*-Pr–	3.0	A-6	2.0	65.6
7	**5**	3.0	A-2	9.0	61.2 (67[2c])
8	**5**	3.0	A-3	9.0	62.3
9	**5**	3.0	A-5	9.0	64.5
10	**5**	3.0	A-6	2.0	69.3
11	*p*-Me–Ph–	3.0	A-3	15.0	46.6 (41[2c])
12	*p*-Me–Ph–	3.0	A-6	2.5	52.8
13	*p*-O_2N–Ph–	1.0	A-4 (pH 9.0)	2.0	81.3 (80[2c])
14	*p*-O_2N–Ph–	1.0	A-6	2.0	72.2
15	*o*-O_2N–Ph–	1.0	A-4 (pH 9.0)	0.5	52.7 (66[2c])
16	*o*-O_2N–Ph–	1.0	A-6	0.5	50.4
17	*p*-Cl–Ph–	3.0	A-3	10.0	61.3 (44[2c])
18	*p*-Cl–Ph–	3.0	A-6	2.0	75.9
19	**6**	1.1	A-1 (pH 9.5)	0.75	79.7[c] (60[2d])
20	**6**	1.1	A-7 (pH 9.5)	0.75	77.5[2d]
21	**7**	1.2	A-1 (pH 9.5)	1.5	63.2[c] (65[2d])
22		1.1	A-1 (pH 9.5)	1.5	45.4[c] (22[2d])

a) All the reactions were carried out by the use of **1** (2.600 g, 10 mmol). b) The yields shown in parentheses correspond to those obtained by the B procedure. c) These products were isolated as the corresponding deblocked derivatives.

A-3: The resultant mixture treated in such a way as in A procedure was stirred with the amount of the ion-exchange resin corresponding to that of being packed in a column of 3×9 cm in water to adsorb the corresponding product (batchwise operation), after which the resin was transfered into a column and the column was washed and eluted successively in the same way as has been described in A procedures. A-4: The condensation reaction was carried out in aqueous methanol (50 ml+50 ml), and the resultant mixture was treated as has been described in A-3. A-5: Prior to the admixture with aqueous acetic acid in A-2 procedure, the resultant reaction mixture was mixed with 50 ml of *N*,*N*-dimethylformamide. A-6: In place of methanol in A-2 procedure, aqueous *N*,*N*-dimethylformamide (50 ml+50 ml) was used as the solvent for the condensation. A-7: The volume of water (5000 ml) for washing in A-1 procedure was reduced to 1000 ml.

In the above connection, an extension of the A procedure was, with some modifications, attempted with respect to a variety of aldehydes; the reaction conditions, the details of the A procedures, and the yields of the hydroxy amino acids are summarized in Table 2. To homogenize the reaction systems, aqueous methanol, methanol, aqueous DMF, and DMF were used as solvents for the condensation reactions besides water. Moreover, a batchwise operation was found to be effective for the cases affording corresponding copper(II) complexes less soluble in water in order to adsorb the corresponding hydroxy amino acids on the ion-exchange resin. Furthermore, the addition of DMF to the resulting mixture prior to its treatment on the column of the resin was found to be more advantageous than the batchwise operation, and the use of DMF as the solvent for the condensation reaction was found to be exceedingly advantageous because of its eminent shortening effect in the reaction period. Thus, the set of improved procedure was confirmed to be sufficiently applicable to the preparation of a variety of hydroxy amino acids.

Experimental

All the hydroxy amino acids obtained herewith were respectively identified with the corresponding authentic specimens.[2c,d] The preparation of DL-threonine will be described as a representative of the set of improved procedures.

DL-Threonine. A mixture of *N*-pyruvylideneglycinatoaquocopper(II) (**1**) (2.600 g, 10 mmol) and acetaldehyde (0.85 ml, 15 mmol) in water (50 ml) was stirred at pH 9.8 at room temperature for 2 hr. After the reaction, the pH of the resultant reaction mixture was adjusted to 4.5 with a 5 M aqueous acetic acid solution.

The resultant solution was then treated by the A-1 procedure and poured onto a column (3×9 cm) of Amberlite IR-120B (H form). The column was washed with distilled water (5000 ml) and successively eluted with a 0.5 M aqueous ammoniacal solution (2000 ml). The effluent was concentrated *in vacuo* almost to dryness, and the residue was treated with ethanol (10 ml) to give white crystals of DL-threonine (1.042 g, 87.6%). Mp 216 °C (dec) [lit,[2c] 216 °C (dec)].

References

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2) a) T. Ichikawa, S. Maeda, Y. Araki, and Y. Ishido, *J. Amer. Chem. Soc.*, **92**, 5514 (1970); b) T. Ichikawa, T. Okamoto, S. Maeda, S. Ohdan, Y. Araki, and Y. Ishido, *Tetrahedron Lett.*, **1971**, 79; c) T. Ichikawa, S. Maeda, T. Okamoto, Y. Araki, and Y. Ishido, This Bulletin, **44**, 2779 (1971); d) S. Ohdan, T. Okamoto, S. Maeda, T. Ichikawa, Y. Araki, and Y. Ishido, *ibid.*, **46**, 981 (1973).