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Synthetic Studies of Amino Acids by the Use of Copper(II) Complex. III. Syntheses of Several 2-Amino-2-deoxyaldonic Acids by the Use of Bisglycinato- and *N*-Pyruvylideneglycinatoaquocopper(II)

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A comparative study of the relative reactivity of bisglycinatocopper(II) and *N*-pyruvylideneglycinatoaquocopper(II) in a base-catalyzed condensation reaction with aldehydo sugar derivatives concluded that the latter complex is much more reactive than the former. This reaction was found to proceed with a considerably high stereoselectivity to afford blocked 2-amino-2-deoxyaldonic acids with a *threo* configurational relationship between *C*-2 and *C*-3, and between *C*-3 and *C*-4. The resultant products were converted to the corresponding free 2-amino-2-deoxyaldonic acids in good yields by deblocking them with Amberlite IR-120B(H form).

In the preceding papers,[1] a new procedure for synthesizing *β*-hydroxy amino acids and 2-amino-2-deoxyaldonic acids involving the base-catalyzed condensation reaction of *N*-pyruvylideneglycinatocopper(II) complexes with a variety of aldehyde species has been reported. An investigation of the syntheses of some 2-amino-2-deoxyaldonic acids by the above

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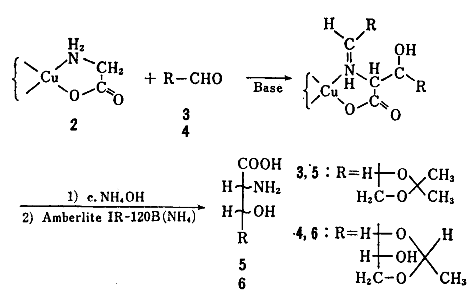
[1] a) T. Ichikawa, S. Maeda, Y. Araki, and Y. Ishido, *J. Amer. Chem. Soc.*, **92**, 5514 (1970); b) T. Ichikawa, T. Okamoto, S. Maeda, S. Ohdan, Y. Araki, and Y. Ishido, *Tetrahedron Lett.*, **1971**, 79; c) T. Ichikawa, S. Maeda, T. Okamoto, Y. Araki, and Y. Ishido, This Bulletin, **44**, 2779 (1971).

procedure was undertaken on the basis of the fact that the reaction is applicable to aldehydes susceptible to isomerization or polymerization under strongly basic conditions,[1] and the discovery of polyoxins,[2] which have been demonstrated to involve 2-amino-2-deoxy-L-xylonic acid and 5-amino-5-deoxy-D-alluronic acid as their constituents.

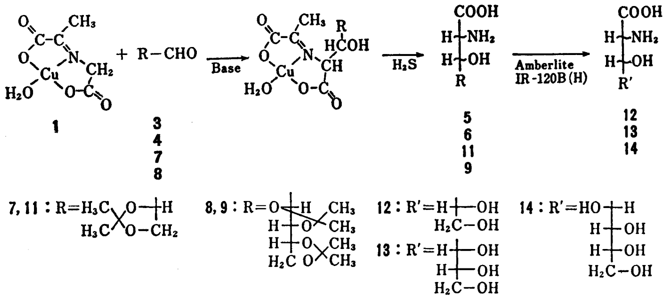
Results and Discussion

The Condensation Reaction with Bisglycinatocopper(II). To elucidate the excellence of the procedure utilizing *N*-pyruvylideneglycinatoaquocopper(II)[1] (**1**) in comparison with that utilizing bisglycinatocopper(II)[3] (**2**), the base-catalyzed condensation reactions of **2** with 2,3-*O*-isopropylidene-D-glyceraldehyde (**3**) and with 2,4-*O*-ethylidene-*al*-D-erythrose (**4**) were examined first.



The reaction of **2** (10 mmol) with **3** (80 mmol) was carried out at 48—50°C, keeping the pH of the mixture at 10.7 by the drop-by-drop addition of an aqueous sodium hydroxide solution during the reaction; this gave 2-amino-2-deoxy-4,5-*O*-isopropylidene-D-aldopentonic acid (**5**) in a 31% yield. Similarly, 2-amino-2-deoxy-4,6-*O*-ethylidene-D-aldohexonic acid (**6**) was obtained in a 22% yield from the reaction of **2** with **4**. The application of **2** to the reaction involving such aldehydo sugars was abandoned since the reaction requires an excess amount of the aldehyde species because of the formation of a Schiff-base-type intermediate in the course of the reaction, and since the yields of the reactions are not very good.

The Condensation Reaction with N*-Pyruvylideneglycinatoaquocopper(II).* On the basis of the above results, the syntheses of 2-amino-2-deoxyaldonic acids were scrutinized by the base-catalyzed condensation reaction of **1** with almost equimolar amounts of **3**, **4**, 2,3-*O*-isopropylidene-L-glyceraldehyde (**7**), and 2,3;4,5-di-*O*-isopropylidene-*al*-D-arabinose (**8**) respectively. In contrast with the reaction of **2**, in which an excess amount of aldehyde species have been utilized, the reaction of **1** with all these aldehydes was completed within 60 min, even at pH 9.5, at room temperature to afford the corresponding 2-amino-2-deoxyaldonic acids with blocking groups in good yields. These results are summarized in Table 1. **3** (Run 1), **4** (Run 2) and **8**(Run 4) gave **5**, **6**, and 2-amino-2-deoxy-4,5;6,7-di-*O*-isopropylidene-D-aldoheptonic acid (**9**) in 70, 70, and 60% yields respectively. On the other hand, the reaction of **1** with **7**(Run 3) assumed a different aspect in contrast with those with other aldehydro sugars. Raw **7**, which was prepared by the lead-tetraacetate oxidation of 4,5-*O*-isopropylidene-L-arabinose dibenzyl dithio acetal,[4] followed by the condensation of the solution *in vacuo*, gave no product. This fact was deduced to arise from the decomposition of **1** by interaction with glyoxal 1,1-dibenzyl dithio acetal (**10**), which was co-produced in the course of the oxidation. On the basis of this fact, a variety of attempts at the separation of **7** from **10** were made. 2-Amino-2-deoxy-4,5-*O*-isopropylidene-L-aldopentonic acid(**11**) was obtained in a 36% yield by the use of a raw sirup of **7** which had been prepared by the concentration of a lead diacetate-free benzene solution of **7**, followed by repeatedly removing the viscous precipitates produced during the evaporation of methanol from the methanolic aqueous solution of the above residual sirup. No more effective procedure was evolved in spite of further attempts at the purification of **7**. The purification by high-vacuum distillation or by chromatography on a column of silica gel gave a material no longer reactive in the condensation reaction. An attempt at the removal of **10** by treating the oxidation mixture with such metal halides as cupric chloride or mercuric bromide was unsuccessful, and the extraction of **7** from the raw sirup with methylene chloride or benzene also resulted in failure. Fortunately, no such trouble accompanied the reactions of **4** or **8** with **1** since they were easily separated from the co-produced sodium formate by repeating the treatment of the raw sirup with ethanol followed by filtration and concentration, or were easily separated from formaldehyde by extraction with methylene chloride from the periodate oxidation mixture.



Subsequently, we attempted to remove blocking groups of the above 2-amino-2-deoxyaldonic acid derivatives by the use of Amberlite IR-120B(H form) in water. By the treatment of **5**, **6**, and **9** with the resin, 2-amino-2-deoxy-D-aldopentonic acid(**12**), -D-aldohexonic acid(**13**), and -D-aldoheptonic acid(**14**) were obtained in 87, 85, and 76% yields respectively. **12**, **13**, and **14** were prepared similarly from **3**, **4**, and **8** without the isolation of **5**, **6**, and **9** by the base-catalyzed condensation reaction, followed by this deblocking procedure; this resulted in 22, 60, and 65% yields respectively. In the first case, the filtrate of crystallization was found by tlc examination still to contain a considerable amount of **12**;

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[2] K. Isono, K. Asahi, and S. Suzuki, *J. Amer. Chem. Soc.*, **91**, 7490 (1969).

[3] M. Sato, K. Okawa, and S. Akabori, This Bulletin, **30**, 937 (1957).

[4] S. B. Baker, *J. Amer. Chem. Soc.*, **74**, 827 (1952).

Table 1. Base-catalyzed condensation reaction of *N*-pyruvylideneglycinatoaquocopper(II) with *aldehydo*-sugar derivatives[a]

Run	*aldehydo*-Sugars	Molar Ratio, R-CHO/**1**	Reaction Time, min	Products			
					Mp(decomp), °C	$[\alpha]_D$(c 1.0, H_2O) (at t°C)	Yield, %
1	**3**[b]	1.1	60	**5**	198	+0.2°(25°C)	70
2	**4**	1.1	40	**6**	209	−0.3°(25°C)	70
3	**7**	1.1	60	**11**	198	−0.2°(20°C)	36
4	**8**	1.2	40	**9**	212	+1.3°(20°C)	60

a) These reactions were carried out by the use of 9 mmol of *N*-pyruvylideneglycinatoaquocopper(II) (**1**) at pH 9.5.
b) The yield of this reaction has been reported in a previous paper (*cf.* 1c).

Table 2. Deblocking of 2-amino-2-deoxy-4,5-*O*-isopropylidene-D-xylonic acid (**5**), -4,6-*O*-ethylidene-D-gluconic acid(**6**), and -4,5;6,7-di-*O*-isopropylidene-D-aldoheptonic acid (**9**) by the use of amberlite IR-120B (H form)

Materials	Products	Mp(decomp), °C	Specific Rotation in H_2O	Yield,[a] %
5	2-Amino-2-deoxy-D-xylonic acid(**12**)	160	$[\alpha]^{20}_{D}-3.9°$ (c 1.9)	82(22)
6	2-Amino-2-deoxy-D-gluconic acid(**13**)	245	$[\alpha]^{20}_{D}+3.7°$ (c 1.0)	85(60)
9	2-Amino-2-deoxy-D-aldoheptonic acid(**14**)	180	$[\alpha]^{22}_{546}+0.2°$ and $[\alpha]^{22}_{578}\simeq 0°$ (c 2.0)	76(65)

a) The data in parentheses are the yields in the preparations without isolation of **5**, **6**, or **9** from the reaction of **1** with the corresponding *aldehydo*-sugars followed by the deblocking procedure.

Table 3. Stereoisomeric composition in the reaction products calculated from the area of chromatograms obtained by the amino acid analysis

Observed Peaks[a]	*aldehydo*-Sugar Derivative Used for the Reaction					
	3[b]	**3**[c]	**4**[b]	**4**[c]	**8**[b]	**8**[c]
A	0.03	0.02	0.02	0.01	0.15	—
B	0.17	0.17	0.12	0.02	0.20	0.05
C	1 (**5**)	1 (**12**)	1 (**6**)	1 (**13**)	1 (**9**)	1 (**14**)
D	0.13	0.14	—	—	0.09	0.07

a) The terms of A, B, C, and D are arbitrary given to the peaks in the chromatograms in the order of their appearence, and C always stands for the main peaks.
b) These mixtures were obtained by the condensation reaction of **1** with *aldehydo*-sugar derivatives.
c) These mixtures were obtained by the condensation reaction followed by the deblocking procedure.

however, no more crystalline product could be obtained. These results are summarized in Table 2.

Subsequently, the stereoisomeric composition of each product was examined by amino-acid analysis in order to examine the possibility that the potential four stereoisomers, which are expected to be formed in this reaction, might be detected easily. These results are summarized in Table 3. Three or four peaks were obviously detected in every chromatogram; the ratios demonstrated in the table were calculated from the ratios of area in the corresponding chromatogram of amino-acid analysis. In view of these data, and supposing that these ratios stand for the actual compositions in each product, it is very interesting that all the reactions proceed with a considerably high stereoselectivity; hence, an important clue for the elucidation of the steric course of the reaction may be obtained by determining the configuration at *C*-2 and *C*-3 in each main product. **12** was confirmed to be 2-amino-2-deoxy-D-xylonic acid on the basis of its behavior in the amino-acid analysis (it behaved just like 2-amino-2-deoxy-L-xylonic acid),[2] and **13** was identified with 2-amino-2-deoxy-D-gluconic acid[5] by a mixed-melting-point determination and by IR spectroscopy. On the basis of these facts, the stereochemistry in **12** and **13** among *C*-2, *C*-3, and *C*-4 were confirmed; they are all *threo* to each other.[6] The stereochemistry in **9** or **14**, in analogy with the above facts, was thought to have the same relation, although there is no decisive evidence at present.[7] These products were found by amino-acid analysis to be identical with the main products observed in each chromatogram.

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[5] M. L. Wolfrom and M. J. Cron, *ibid.*, **74**, 1715 (1952).

[6] Further investigations with close attention to some potential factors were required to elucidate the steric course of the reaction mechanism involving a variety of aldehydes which are variously substituted. A tentative proposal on the mechanism has been made in Dr. Thesis of T. Ichikawa, Tokyo Institute of Technology (1971, March).

[7] The stereochemistry of this compound will be confirmed by deriving into the corresponding 2-amino-2-deoxy-D-aldoheptose. The investigation is now in progress along with **12** and **13**.

Experimental

All the melting points are uncorrected. Amino-acid analyses were carried out by means of a Hitachi KLA-3B Amino-acid Analyzer. The specific rotations were determined by means of a Carl-Zeiss Photoelectric Precision Polarimeter (0.005°) at 546 and 578 nm, and the $[\alpha]_D$ values were calculated by the use of Drude's equation.

*The Condensation Reaction with Bisglycinatocopper(II). The Reaction of Bisglycinatocopper(II) (**2**) with 2,3-*O*-Isopropylidene-D-glyceraldehyde (**3**).* To a solution of 1,2;5,6-di-*O*-isopropylidene-D-mannitol[8] (10.4 g, 40 mmol) in water (120 ml), we added, portion by portion, sodium metaperiodate (8.8 g, 40 mmol), keeping the temperature at 25°C; the solution was then stirred at room temperature for 30 min. The precipitated sodium iodate was filtered off, and the filtrate was concentrated *in vacuo* below 40°C almost to a sirup. When the sirup was treated with ethanol (20 ml), the sodium iodate further precipitated was removed by filtration. This operation was repeatedly carried out in order to remove the small amount of sodium iodate remaining in the sirup. To a solution of the resultant sirup in water (total volume: 60 ml), we added **2**[3] (2.30 g, 10 mmol); the resultant mixture was stirred for 1 hr at room temperature, keeping the pH at 10.7 by the drop-by-drop addition of a 1 M aqueous sodium hydroxide solution. Then, the resultant mixture was treated with a concentrated aqueous ammoniacal solution to decompose the complex of 2-amino-2-deoxy-4,5-*O*-isopropylidene-D-xylonic acid (**5**), after which the solution was treated on a column (2.5×7 cm) of Amberlite IR-120B (NH_4 form). The column was then washed with water (500 ml). The light yellow effluent was evaporated *in vacuo* to a volume of *ca.* 20 ml, and the concentrate was extracted with methylene chloride (10 ml×3). The aqueous layer was further concentrated *in vacuo* to a volume of *ca.* 5 ml, and the concentrate was treated with several milliliters of methanol to afford **5** (1.27 g, 31%). Mp 201—202°C (decomp.) [lit.[1c] 198°C (decomp.)].

*The Reaction of **2** with 2,4-*O*-Ethylidene-*al*-D-erythrose (**4**).* To a solution of 4,6-*O*-ethylidene-D-glucopyranose[9] (8.4 g, 40 mmol) in water (100 ml), sodium metaperiodate (17.6 g, 80 mmol) was portion by portion added, under cooling with ice water. During this operation, the pH of the mixture was kept at 4—5 by the addition of crystalline sodium bicarbonate. After the removal of the resultant salts in the same way as above, the solution of **4** was similarly subjected to the reaction with **2**. When the resultant mixture was treated in a similar manner, 2-amino-2-deoxy-4,6-*O*-ethylidene-D-gluconic acid (**6**) (0.96 g, 22%) was obtained. Mp 209°C (decomp.). Found: C, 43.54; H, 6.97; N, 6.54%. Calcd for $C_8H_{15}NO_6$: C, 43.43; H, 6.84; N, 6.33%.

*The Condensation Reaction with N-Pyruvylideneglycinatoaquocopper(II). The Reaction of N-Pyruvylideneglycinatoaquocopper(II) (**1**) with 2,3-*O*-Isopropylidene-L-glyceraldehyde (**7**):* To a solution of 4,5-*O*-isopropylidene-L-arabinose dibenzyl dithio acetal[4] (4.2 g, 10 mmol) in benzene (80 ml), we added lead tetraacetate (4.7 g, 11 mmol); the solution was then stirred at room temperature for about 30 min. The precipitate was filtered off, and the filtrate was concentrated *in vacuo* below 40°C to a sirup. After the dissolution of the sirup in methanol (20 ml), distilled water (20 ml) was added. The solution was concentrated again *in vacuo* below 40°C to a volume of *ca.* 20 ml. The resultant sirupy precipitate was filtered off, and the filtrate was concentrated to a volume of 10 ml. To a solution of L-glyceraldehyde thus prepared, **1** (2.30 g, 9 mmol) was added together with water (30 ml); the pH of the resultant mixture was adjusted to 9.5 by the addition of a 2 M aqueous sodium hydroxide solution. Then, the mixture was stirred at room temperature for 1 hr, keeping its pH at 9.5. After the reaction, the resultant solution was adjusted at pH 4.5 with a 2 M aqueous hydrochloric acid solution and treated with hydrogen sulfide gas; the resultant precipitate was filtered off. The filtrate was immediately treated on a column (2.5×9 cm) of Amberlite IR-45 (OH form), and the column was washed with water (100 ml). The effluent was concentrated to a volume of *ca.* 50 ml, and the concentrate was treated on a column (2.5×9 cm) of Amberlite IR-120B (NH_4 form). Then, the column was washed with water (100 ml). The effluent was concentrated to a volume of *ca.* 50 ml, and the concentrate was washed with methylene chloride (10 ml×3). The aqueous layer was then concentrated *in vacuo* to a volume of *ca.* 10 ml. The treatment of the concentrate with several milliliters of ethanol gave raw crystals, which were subsequently recrystallized from aqueous ethanol to give 2-amino-2-deoxy-4,5-*O*-isopropylidene-L-aldopentonic acid (**11**) (0.65 g, 36%).

Mp 198°C (decomp.). $[\alpha]^{20}_{D}$ −0.2° (*c* 1.0, H_2O). Found: C, 46.61; H, 7.51; N, 6.66%. Calcd for $C_8H_{15}NO_5$: C, 46.82; H, 7.37; N, 6.83%.

*The Reaction of **1** with 2,4-*O*-Ethylidene-*al*-D-erythrose (**4**):* To a solution of **4**, which had been prepared from 4,6-*O*-ethylidene-D-glucopyranose (2.1 g, 10 mmol) in the way described previously, in water (50 ml), we added **1** (2.30 g, 9 mmol) together with water (30 ml); the mixture was then stirred at room temperature for 40 min, keeping the pH at 9.5 by the drop-by-drop addition of a 1 M sodium hydroxide solution. After the reaction, the resultant mixture was treated in the same way described in the previous experiment, and the resultant raw crystals were recrystallized from aqueous ethanol to give **6** (1.40 g, 67%). Mp 209°C (decomp.).

*The Reaction of **1** with 2,3;4,5-Di-*O*-isopropylidene-*al*-D-arabinose (**8**):* To a solution of 1,2;3,4-di-*O*-isopropylidene-D-mannitol (2.6 g, 10 mmol)[10] in water (50 ml) we added sodium metaperiodate (2.2 g, 10 mmol); the solution was then stirred at room temperature for 30 min, keeping the pH at 4—4.5 by the addition of sodium bicarbonate. The solution was then extracted with methylene chloride (50 ml×10), and the extract was concentrated *in vacuo* below 40°C almost to a sirup. The resultant sirup was subjected to a reaction with **1** (2.30 g, 9 mmol) (reaction time: 40 min) and treated in the same way as above to give 2-amino-2-deoxy-4,5;6,7-di-*O*-isopropylidene-D-aldoheptonic acid (**14**) (1.85 g, 60%).

Mp 212°C (decomp.) (recrystallized from aqueous ethanol). Found: C, 50.86; H, 7.56; N, 4.78%. Calcd for $C_{13}H_{23}NO_7$: C, 51.14; H, 7.59; N, 4.59%.

*Deblocking of **5**:* An aqueous solution of **5** (2.83 g, 13.7 mmol) in water (200 ml) was treated on a column of Amberlite IR-120B (H form) (3×9 cm), after which the column was washed with water (2000 ml). Then, the column was eluted with a 0.5 M aqueous ammoniacal solution (2000 ml), and the effluent was concentrated *in vacuo* to a volume of *ca.* 10 ml. The concentrate was treated with methanol (10 ml) to give crystals of 2-amino-2-deoxy-D-xylonic acid (**12**) (1.98 g, 87%). Mp 160°C (decomp.). $[\alpha]^{25}_{D}$ −3.4° (*c* 1.9, H_2O). Found: C, 36.41; H, 6.95; N, 8.48%. Calcd for $C_5H_{11}NO_5$: C, 36.36; H, 6.71; N, 8.48%.

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8) D. Horton, J. B. Hughes, and J. K. Thompson, *J. Org. Chem.*, **33**, 728 (1968).

9) R. Barket and D. L. MacDonald, *J. Amer. Chem. Soc.*, **82**, 2301 (1960).

10) L. F. Wiggings, *J. Chem. Soc.*, **1946**, 13.

*Deblocking of **6***: To a solution of **6** (10g, 45 mmol) in water (300 ml), we added Amberlite IR-120B (H form) (200 ml); the mixture was then stirred at room temperature for 24 hr.[11] The complete adsorption of **6** to the resin was examined by means of the ninhydrin test. The resin was then packed in a column (d: 2.5 cm), and the column was washed with water (1000 ml) and subsequently eluted with a 1 M aqueous ammoniacal solution (500 ml). The effluent was concentrated *in vacuo* to a volume of about 10 ml, and the concentrate was treated with several milliliters of ethanol to give 2-amino-2-deoxy-D-gluconic acid (**13**) (7.5 g, 85%). Mp 245°C (decomp.). This sample showed no depression on admixture with an authentic specimen.[5] $[\alpha]^{20}_{D}$ +3.7° (*c* 1.0, H_2O). The IR spectrum of this sample was also in complete agreement with that of the specimen.[5] Found: C, 36.64; H, 6.82; N, 7.17%. Calcd for $C_6H_{13}NO_6$: C, 36.92; H, 6.71; N, 7.18%.

*Deblocking of **9***: A solution of **9** (3.0 g, 10 mmol) in water (200 ml) was treated in the same way as has been described for the deblocking of **5** to give 2-amino-2-deoxy-D-aldopentonic acid (**14**) (1.7 g, 76%). Mp 180°C (decomp.). $[\alpha]^{22}_{546}$ +0.2° and $[\alpha]^{22}_{578} \simeq 0°$ (*c* 2.0, H_2O). Found: C, 37.21; H, 6.49; N, 6.36%. Calcd for $C_7H_{15}NO_7$: C, 37.33; H, 6.71; N, 6.22%.

*Preparation of **12**, **13**, and **14** without the Isolation of **5**, **6**, and **9** Respectively.* *Preparation of **12***: The mixture resulting from the base-catalyzed condensation reaction of **1** with **3**, which has been described in a previous paper,[1c] was adjusted at pH 4.5 with a 5 M aqueous acetic acid solution and then treated with hydrogen sulfide gas. The precipitated cupric sulfide was removed by filtration, and the filtrate was treated on a column of Amberlite IR-120B (H form) (3×9 cm). The column was washed with water (1000 ml) and then eluted with a 0.5 M aqueous ammoniacal solution (1000 ml). The effluent was concentrated *in vacuo* to a volume of *ca.* 10 ml, and the concentrate was treated as has been described previously to give **12** in a 22% yield.

*Preparation of **13***: The mixture resulting from the reaction of **1** with **4**, which has been described as the fourth example in this section, was treated in the same way as above, except that the washing procedure after the adsorption of **6** on the resin was done with 5000 ml of water. Yield, 60%.

*Preparation of **14***: The mixture resulting from the reaction of **1** with **8**, which has been described as the fifth example in this section, was treated in the same way as that used in the preparation of **12**. Yield, 65%.

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[11] Unless this operation is done under possibly gentle stirring, the resin was ground into small particles, and the washing and the elution procedures got into difficulties. Moreover, these operations came to need much voluminous solvents, and the yield of **13** was considerably lowered.