ture) M^+ (rel intensity, 22, nine-line pattern for 8 Br) $(Br_2C{=}N{=}CBr_2)^+$ (100).

Anal. Calcd for $C_6H_2N_2Br_8$: C, 9.72; H, 0.27, N, 3.78; Br, 86.23. Found: C, 9.55; H, 0.25; N, 3.64; Br, 86.39.

2-Aza-3-phenyl-1,1,4,4-tetrabromo-1,3-butadiene (6). A sample of azoethene **2** (1.0 g, 1.8 mmol) was heated neat in a test tube to 190°. The black mass obtained was cooled and 5 ml of methanol was added. White square platelets (0.65 g, 80%) of azabutadiene **6** were obtained, mp 60° (MeOH). The liquid droplets condensed on the test tube wall were shown to be benzonitrile by ir.

Similarly, **6** was prepared by heating a solution of **2** (1.0 g, 1.8 mmol) in chlorobenzene at reflux for 4 hr until the originally deep red solution was practically colorless, evaporation of the solvent, and trituration with MeOH: yield 0.80 g of **6** (100%, 71% after MeOH); ir (CCl_4) 3062, 1674, 1623, 1490, 1447, 1060, 870, 697, 650 cm^{-1}; uv (methanol) end absorption; NMR (CCl_4) τ 2.61 (apparent s); MS (100 eV, 150° probe temperature) M^+ (rel intensity, 14, five-line pattern for 4 Br), $(M - Br_2CN)^+$ (100).

Anal. Calcd for $C_9H_5NBr_4$: C, 24.19; H, 1.13; N, 3.14; Br, 71.54. Found: C, 24.19; H, 1.25; N, 3.13; Br, 71.35.

Bromine Generation from Ketazine 3. A solution was prepared containing 12 g (0.033 mol) of ketazine **3** in 20 ml of *o*-dichlorobenzene in a 50-ml round-bottomed flask connected to a trap containing methylene chloride at 0°. The solution was heated at 150–170° for 30 min with a nitrogen stream bubbling through the system. The bromine collected in the trap was titrated with 850 mg of cyclohexene (10.3 mmol, 77%) and azopropene **5** (8.8 g, 89%) was recovered as a crystalline solid.

Registry No.—**2**, 56454-39-8; **3**, 56454-40-1; **4**, 56454-41-2; **5**, 56454-42-3; **6**, 56454-43-4; acetophenone azine, 729-43-1; bromine, 7726-95-6; acetone azine, 627-70-3.

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A Novel High-Yield Synthesis of γ Esters of Glutamic Acid and β Esters of Aspartic Acid by the Copper-Catalyzed Hydrolysis of Their Diesters

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Benzyl esters have a unique place in peptide synthesis for the reversible protection of side-chain carboxyl groups.[1] These esters are relatively stable to the mildly acidic and basic conditions of peptide synthesis, but can be easily removed at the end of the synthesis by strongly acidic or reductive cleavage.[2] A problem with benzyl esters, however, is that they are not completely stable to reagents commonly used to remove the α-NH_2 *tert*-butyloxycarboxyl protecting group (e.g., trifluoroacetic acid–dichloromethane, 1:1) and are slowly hydrolyzed by these reagents.[3]

This lability can cause difficulties in long syntheses, giving rise to cumulative loss of side-chain protection and hence to branching of the peptide chain. To prevent the occurrence of this problem, more stable carboxyl-protecting groups are needed. These groups are also useful for the solid-phase synthesis of protected peptide fragments, which can be achieved by the use of side-chain protecting groups[4] which are completely stable to the reagents used to cleave the peptide from the resin (e.g., HBr in acetic acid).

For these reasons, substituted benzyl esters have been used by several workers[5–7] for side-chain carboxyl protection, although the use of such esters has been hindered by a lack of methods for their facile preparation. For example, the *p*-nitrobenzyl esters of Schwarz and Arakawa[5] can best be prepared by the procedures of Ledger and Stewart,[6] which involve the preparation of the copper complex of the amino acid, and the subsequent esterification of this copper complex with *p*-nitrobenzyl halide. This method is lengthy, however, and yields are low. The selective hydrolysis of aspartic and glutamic acids diesters which is described in this communication provides a method for the preparation in high yield of a wide range of monoesters by a very simple procedure.

In this procedure the amino acid is converted to the appropriate diester salt, using well-established procedures.[1,8,9] Without further purification the diester is then hydrolyzed by aqueous copper sulfate, and the copper complex of the desired monoester is isolated by filtration. After the copper complex has been decomposed with EDTA by the method of Ledger and Stewart,[6] the monoester can be isolated in a pure form by a single recrystallization.

In a typical copper hydrolysis, glutamic acid dibenzyl ester *p*-toluenesulfonate (10 g, 20 mmol) was dissolved in ethanol (140 cm^3) and aqueous $CuSO_4 \cdot 5H_2O$ (20 g, 80 mmol in water, 350 cm^3) was added. The pH was raised to 8.0 with 1 *M* NaOH, and the solution was maintained at that pH and 32°C for 60 min. The pH was then lowered to 3.0 with 3 *M* HCl and the precipitate of the copper complex of Glu(γOBzl)[10,11] was filtered off and washed with water, ethanol, and ether. Ethylenediaminetetraacetic acid disodium salt (7.8 g, 21 mmol) in 100 cm^3 of water was added, the solution was boiled and filtered, and on cooling, glutamic acid γ-benzyl ester precipitated out. The product was collected by filtration and washed with water, ethanol, and ether: yield 3.5 g (14.8 mmol, 74%); mp 169–170°; $[\alpha]^{22}D$ +19.3° (*c* 5.49, acetic acid) (lit. mp 169–170°, $[\alpha]^{25}D$ +19.2).[6]

The yields for various esters of glutamic and aspartic acids are given in Table I.

Terashima et al.[12] have proposed a structure for the copper complexes of aspartic and glutamic acids where both the amino nitrogen and one of the carboxyl oxygens are coordinated to the copper atom only if a five-membered ring is formed. This proposal was confirmed by the absence in the hydrolysis product of any trace of the α-monoesters of aspartic and glutamic acid or of the free amino acids.[13]

The mechanism of the copper-catalyzed hydrolysis of amino acid esters has been suggested[14] to proceed by OH^- attack on the carbonyl group of the copper coordinated ester linkage. If this is the case, the rate of hydrolysis should be increased by electron-withdrawing substituents on the ester group. To test this hypothesis, the rate of the copper hydrolysis reaction for various glutamic acid diesters was measured. Samples of the reaction mixture were quenched with dilute acid, treated with EDTA, and chromatographed on silica gel plates, using a 1-butanol–acetic acid–pyridine–water (15:3:10:12) solvent. The γ-ester spots

Table I
Yield of Asp and Glu Diesters Prepared by the Copper-Catalyzed Hydrolysis of Corresponding Diesters

Ester	Crude yield,[a] mol %	Yield of recrystd ester, mol %	Mp, °C	Lit. mp, °C	Registry no.
Glu (OBzl)	95	74	169–170	169–170[b]	1676-73-9
Glu (OBzl-*p*-Cl)	93	54[c]	169–170	176[d]	20806-20-6
Glu (OBzl-*p*-NO_2)	87	54[c]	158–159[e]	171–172[f]	3940-62-3
Glu (OMe)	99		180[d]	182[d,g]	1499-55-4
Glu (OEt)	96		192–194	194[g]	1119-33-1
Asp (OBzl)	98	67	220–222	221[h]	2177-63-1
Asp (OBzl-*p*-Cl)	98	83	208–210	208[h]	14335-22-9
Asp (OBzl-*p*-NO_2)	97	88	193–195	189–190[f]	3940-63-4
Asp (OMe)	98		188–190[i]	191–193[g,i]	2177-62-0

[a] Measured by TLC of an aliquot of the reaction mixture. [b] J. Noguchi, *Chem. Abstr.*, **59**, 10238 (1963). [c] The reduced yield of these esters is possibly due to their very low solubility in all common solvents. [d] M.-H. Loucheux and M. J. Parrod, *C. R. Acad. Sci., Ser. C*, **267**, 614 (1968). [e] It has been observed that this compound may show more than one distinct melting point, presumably because of the existence of several crystalline forms. [f] Reference 6. [g] Reference 1, p 929. [h] M. Hashimoto and J. Aritomi, *Bull. Chem. Soc. Jpn.*, **39**, 2707 (1966). [i] As hydrochloride.

Table II
Rate Constants for the Cu(II)-Catalyzed Hydrolysis of Glutamic Acid Diesters

Diester	Rate[a], min^{-1}	Registry no.
Glu (OBzl-*p*-NO_2)$_2$	0.54	47662-90-8
Glu (OBzl)$_2$	0.54	2768-50-5
Glu (OBzl-*p*-Cl)$_2$	0.14	56437-39-9
Glu (OMe)$_2$	0.070	6525-53-7
Glu (OEt)$_2$	0.067	16450-41-2
Glu (OEt 2-Cl)$_2$	0.050	56437-40-2

[a] pH 8, 32°.

were visualized with ninhydrin and the ninhydrin color eluted with ethanol and measured at 250 nm. The rates of the reaction are given in Table II.

The rates are consistent with the mechanism proposed, in that the ethyl ester reacts more slowly and the benzyl ester more rapidly than the methyl ester. Esters substituted with chlorine, however, react more slowly than do unsubstituted esters, in spite of the electron-withdrawing nature of the chlorine moiety. This anomaly is probably due to the large volume occupied by a chlorine atom, as reactions of amino acid copper complexes appear to be very susceptible to steric hindrance.[12]

Registry No.—Dibenzyl aspartate, 2791-79-9; *p*-chlorodibenzyl aspartate, 56437-41-3; *p*-nitrodibenzyl aspartate, 47636-64-6; dimethyl aspartate, 6384-18-5.

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Simple, Novel Deaminations. VII.[1,2] The High-Yield Conversion of Primary and Secondary Carbinamines to Alcohol and Formate Esters via Nucleophilic Substitution of Protonated Sulfonimide Derivatives

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The conversion of the aliphatic primary amino group to the primary hydroxyl group has been, historically, relatively difficult to achieve. Until now the apparent best yielding procedures (25–90%) involve the pyrolysis of *N*-nitrosoamides[4] or the treatment of arylalkyl triazenes with carboxylic acids.[5] Both of these methods exclusively produce esters as the carbon–oxygen product. To obtain the alcohol, a subsequent ester hydrolysis is obligatory. Moreover skeletal rearrangements are common, although in nonpolar solvents the occurrence of this problem is reduced, presumably because the mechanism in nonpolar solvents is usually SN2.[4-6]

In previous papers in this series,[1-3,7,8] it has been found that various sulfonimide activating groups (1), analogous to various sulfonate ester activating groups in the alcohol series, are readily susceptible to nucleophilic substitution (Scheme I). These processes occur with ease, most probably because sulfonimide anions are weak bases compared to NH_2^- anions, and consequently sulfonimide anions are relatively good leaving groups. For example, in these and other laboratories, primary and secondary carbinamines have been converted, usually in high yields, to alkyl halides,[2,3,8,9] to alkenes,[1-3,7-9] to ketones,[1] and to alkanes[12] and other functional groups.[2,3,8,9,11,13]

Results

However, all our attempts to convert these activated sulfonimide derivatives (1) to alcohols via the use of the hydroxide anion as a nucleophile have been essentially unsuc-